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Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study

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Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study.

Running title: Patients with suspected COVID-19 in general practice

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ABSTRACT

Objectives: To describe and compare the initial clinical characteristics of a cohort of patients with suspected COVID-19 (confirmed, no COVID, and uncertain cases) managed by general practitioners (GPs); to assess whether 3-month persistent symptoms were more frequent among confirmed cases than among no-COVID cases; and to identify factors predictive of persistent symptoms and adverse outcomes among confirmed cases.

Design and setting: A comparative, prospective, multicentre cohort study in primary care, in the Paris region of France.

Participants: 521 patients aged ≥18 with suspected COVID-19 were enrolled between March and May 2020; people under 18 or with no suspicion of COVID-19 or institutionalized were excluded.

Outcome measures: Initial symptoms, COVID-19 status, persistent symptoms 3 months post-inclusion, and a composite criterion for potentially COVID-19-related events (hospitalization, death, emergency department visits).

Results: 516 patients were analyzed; 166 (32.2%) were classified into the "confirmed COVID" group, 180 (34.9%) into the "no-COVID" group and 170 (32.9%) in the "uncertain COVID" group. Confirmed cases had more persistent symptoms than no-COVID cases (*P*=0.09), were more likely to have anosmia (*P*=0.047) and other rare symptoms (*P*=0.071); initial fever/feeling feverish and anosmia were independently associated with persistent symptoms. At 3 months, we observed 16 (9.8%) COVID-19 related hospitalizations, 3 (1.8%) intensive care unit admissions, 13 (37.1%) referrals to an emergency department, and no deaths. Age >70 and/or at least one comorbidity (OR 6.53; 95% CI [1.13-37.84]; *P*=0.036), abnormalities in a lung examination (15.39 [1.61-146.77]; *P*=0.057) and two or more

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systemic symptoms (38.61 [2.30-647.40]; *P*=0.011) were associated with the composite criterion.

Conclusions: Although most COVID-19 patients in primary care had mild disease with a benign course, almost 1 in 6 had persistent symptoms at 3 months. These symptoms were more frequent in the "confirmed COVID-19" group. Our findings need to be confirmed in a prospective study with longer follow-up.

Word count: 299/300

Keywords: COVID-19, signs and symptoms, cohort studies, risk factors, general practice

Strengths and limitations of this study

This work is one of the few French studies to have included solely patients in primary care early on in the first wave of the COVID-19 pandemic.

In contrast to most COVID-19 studies, this study featured a control group: "confirmed COVID-19" patients were compared with "no-COVID-19" and "uncertain COVID-19 patients.

This prospective cohort study was carried out over a short time frame in several primary care health centres; some results might be extrapolable to other settings.

Early on in the pandemic, COVID-19 RT-PCR tests were not widely available. Consequently, COVID-19 status (or not) was not confirmed in all patients.

Individuals under the age of 18 and those living in an institution were not included in the study.

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BACKGROUND

The first wave of COVID-19 in France prompted a lockdown from mid-March to mid-May 2020. General practitioners (GPs) were in the front line [1]; they referred severe cases to hospital and managed less severe cases [2]. Early on in the epidemic, researchers sought to describe the COVID-19 patients' demographic and clinical characteristics and their course of disease. However, these studies were fully [3-8] or partly [9] conducted in hospital. The most frequently reported initial signs were fever, cough, and dyspnoea [3]. Anosmia and ageusia were also prevalent, and their concomitant presence was quite specific for a SARS-CoV-2 infection [10-12]. At the time when our study data were collected, some researchers had highlighted "long COVID-19" as an entity with some or all the following symptoms 3 to 12 months after disease onset [8,13,14]: persistent asthenia, headache, dyspnoea, sleep difficulties, anxiety or depression, and anosmia [13,14]. The significance of these symptoms is subject to debate, particularly since the literature data were somewhat contradictory; however, some researchers have suggested that these symptoms are correlated with the severity of the initial disease [8] and the number of initial symptoms [15]. Most of these studies of "long COVID-19" estimated the frequency of persistent symptoms or adverse outcomes in hospital cohorts of patients with a confirmed diagnosis of COVID-19 but lacked a control group [3,4,7-8]. Hence, these studies were not representative of patients in primary care – even though most COVID-19 cases are diagnosed by GPs [2]. Therefore, the objectives of the present study were to (i) describe and compare the initial clinical characteristics of a cohort of patients with suspected COVID-19 managed by GPs (confirmed cases, no-COVID cases, and uncertain cases); (ii) determine whether persistent symptoms at 3 months were more frequent among confirmed cases than among no-COVID cases; and (iii) identify factors predictive of persistent symptoms and adverse outcomes among confirmed cases.

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METHODS

Study design

This multicentre, prospective cohort study was conducted in four counties in the Paris region: Val-de-Marne, Seine-et-Marne, Essonne, and Seine-Saint-Denis. Forty-four GPs were recruited from multiprofessional primary care practices affiliated with the Faculty of Health at Université Paris-Est Créteil (Créteil, France), because some of the GPs tutored the university's medical students. The GPs' characteristics are summarized in the Online Supplement 1 Table S1.

Population

During the first wave's lockdown period, we prospectively included all consecutive adult patients who consulted one of the participating GPs for a suspected COVID-19 infection. The exclusion criteria were age under 18, no suspicion of COVID-19, and residence in an institution. The first patient was included on March 6th, 2020, and the last was included on May 12th, 2020. Patients were followed up for three months, and study data were extracted on October 22nd, 2020.

Data sources

The patients' data were extracted from the GPs' electronic medical records. The clinical criteria for a diagnosis of COVID-19 were left to the GP's discretion. Patients were followed up as usual by their GP, and all consultations with healthcare professionals and/or hospital visits were registered. Three months after inclusion, the GP phoned or visited patients to collect data on persistent symptoms or recovery. For confirmed cases, they also looked for COVID-19-related hospital admissions, referrals to an emergency department, admissions to

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an intensive care unit, and deaths. These data were completed with information from hospital discharge reports, if available.

COVID-19 status

The GPs prescribed SARS-CoV-2 serology and/or RT-PCR tests and/or a CT scan of the chest, in line with the French national guidelines [16-20]. During the first wave of COVID-19 (mid-March to mid-May 2020), RT-PCR and serology tests were not widely available. An RT-PCR test was recommended for patients with severity criteria and/or with comorbidities, and for healthcare professionals [16-17]. The French national guidelines recommended a CT scan if the patient had trouble breathing, in order to assess the extent of any lung damage and to have a reference examination [20]. Serology tests became available from May 2020 and were prescribed *a posteriori* to (i) patients with compatible symptoms and who had not had an RT-PCR test and (ii) patients with a negative RT-PCR test [17-18].

Each patient's COVID-19 status was classified as "confirmed COVID", "no-COVID", or "uncertain COVID". Confirmed COVID status was defined as a positive RT-PCR and/or serology test, and/or a chest CT result suggestive of COVID-19. "No-COVID" status was defined as both a negative RT-PCR test and a negative serology test, a negative RT-PCR test in the absence of a positive serology test or a positive chest CT, or a negative serology test in the absence of a positive RT-PCR test or a positive chest CT. "Uncertain COVID" status was defined as the presence of suggestive symptoms and the absence of both RT-PCR and serology test and chest CT results.

Outcomes

We considered the two following outcomes: the persistence of symptoms three months after study inclusion (as assessed by the GP), and (for confirmed cases only) adverse outcomes

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defined by a composite criterion that included COVID-19-related hospital admissions, referral to an emergency department, intensive care unit admissions, and deaths. The relationship with COVID-19 was determined from hospital records.

Potential factors predictive of 3-month persistent symptoms and adverse outcomes

Among confirmed cases, the following variables (Table 1) collected at the initial consultation were considered as potentially predictive factors for persistent symptoms and adverse outcomes: demographic characteristics (age, sex, being a caregiver), smoking, obesity, comorbidities, initial COVID-19 symptoms, the number of symptoms, systemic symptoms (i.e., fever, headache, asthenia, and skin symptoms), ENT symptoms, and data from an initial clinical examination.

Statistical analysis

Qualitative variables were described as the number (percentage), and quantitative variables were described as the median [interquartile range (IQR)] or tertile values, as appropriate. Univariate analyses used the chi-2 test, the Fisher's test or the Kruskal-Wallis test, as appropriate. Given the hierarchical nature of the data (level 1: the patient; level 2: the GP), we used multilevel logistic models [21] to estimate univariate and multivariate odds ratios (ORs) and their 95% confidence intervals (CIs).

The distribution of the patient initial characteristics was compared across the three groups (confirmed, no-COVID, and uncertain). When the *P*-value was ≤0.15, we used age-adjusted multilevel logistic models to perform post-hoc pairwise comparisons for confirmed cases vs. no-COVID cases on one hand, and between confirmed cases and uncertain cases on the other. Next, we compared the prevalence of persistent symptoms in the confirmed vs. no-COVID groups. To assess predictive factors for 3-month persistent symptoms and adverse outcomes

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among the COVID confirmed cases, we compared the groups with vs. without persistent symptoms and with vs. without adverse outcomes, in univariate analyses. Factors with $P<0.15$ in the univariable analysis were considered for inclusion in multivariable logistic analyses after the assessment of confounders and interactions in bivariate models. As "older age" and "at least one comorbidity" were highly correlated, we built the following composite variable: "age>70 and/or at least one comorbidity". Lastly, in a sensitivity analysis, patients with both anosmia and ageusia but no test results were moved from the "uncertain COVID-19" group to the "confirmed" group, and similar analyses were performed. All tests were two-sided, and the threshold for statistical significance was set to $P\leq0.05$. We used the false discovery rate method for post-hoc analyses. All analyses were performed with Stata software (version 14.2, StataCorp LLC, College Station, TX, USA).

Ethics

All patients received an information sheet and gave their verbal consent to participation. The study database was registered with the French National Data Protection Commission (reference: 2211627 v0). The study protocol was approved by an independent ethics committee (*Comité de Protection des Personnes Est IV* (Strasbourg, France); reference: IDRCB 2020-A01693-36).

RESULTS

Study population

During the study period, 521 patients were included. Of these, 516 were analysed: 166 (32.2%) were classified as "confirmed COVID", 180 (34.9%) were classified as "no-COVID", and 170 (32.9%) were classified as "uncertain COVID" (Figure 1).

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Characteristics of the population, and intergroup comparisons

In the overall population, median [IQR] age was 43 y [33-56], 62.2% were female, 12% were caregivers, and 40.7% had at least one comorbidity (Table 1). The three groups differed significantly with regard to the following initial characteristics: age, being a caregiver, having been in contact with a positive case, having at least one comorbidity, fever or feeling feverish, having muscle ache, chest pain, dyspnoea, a sore throat, anosmia, agueusia, diarrhoea, and the number of systemic symptoms.

Relative to the no-COVID group, confirmed cases were significantly older and were more likely to be caregivers, to have been in contact with a confirmed case of COVID-19, and to have had anosmia or agueusia. A non-significant trend towards an association with a higher number of systemic symptoms was also observed. In contrast, chest pain and sore throat were less frequent in the "confirmed case" group.

Relative to the uncertain COVID-19 group, confirmed cases were significantly older and were more likely to be caregiver, to have been in contact with a confirmed case of COVID-19, to have had fever or feeling feverish, muscle ache, anosmia, agueusia, diarrhoea and more than two systemic symptoms. In contrast, they were less likely to be male.

Three-month persistent symptoms in the "confirmed COVID" and "no-COVID" groups

Overall, the percentage of three-month persistent symptoms was higher in the confirmed COVID group than in the no-COVID group, although the difference was not statistically significant (P=0.090) (Table 2). The confirmed COVID group was more likely to have persistent anosmia (OR=8.51; 95% CI [1.03-70.43]) and other miscellaneous symptoms (deep vein thrombosis, alopecia, palpitations, myalgia, feeling feverish, and memory impairments) (OR=7.02; 95% CI [0.84-58.29]). Similar results were found in the sensitivity analysis (Table 2).

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Predictive factors for 3-month persistent symptoms and adverse outcomes in confirmed COVID cases

In a univariate analysis, the factors associated with 3-month persistent symptoms were fever or feeling feverish and anosmia (Table 3). In a multivariate analysis, fever and anosmia were independently associated with 3-month persistent symptoms. Similar results were found in the sensitivity analysis (OR_{fever}=8.49; 95% CI [1.34-53.83]; *P*=0,023 and $OR_{anosmia}$=4.24 95%; 95% CI [0.99-18.23]; *P*=0,052).

Among the confirmed cases, we observed 16 (9.8%) COVID-19 related hospitalizations, 3 (1.8%) admissions to an intensive care unit, 13 (37.1%) referrals to an emergency department, and no deaths. In a univariate analysis, patients with 3-month adverse outcomes were older, and more likely to have at least one comorbidity (hypertension, dyslipidaemia, diabetes, and cardiovascular disease), fever or feeling feverish, and a higher number of systemic symptoms (Table 4). A trend was observed for abnormalities in a lung clinical examination. In a multivariate analysis, the composite variable "age >70 and/or at least one comorbidity", abnormalities in a lung clinical examination and two or more systemic symptoms were independently associated with 3-month adverse outcomes (Table 4). Similar results were found in the sensitivity analysis (OR_{fever}=6.72; 95% CI [1.24-36.54]; *P*=0,027; $OR_{\geq 2 \text{ systemic symptoms}}$=44.52; 95% CI[2.67-741.89]; *P*=0,008; and $OR_{\text{abnormalities in a lung examination}}$=17.58; 95% CI [1.80-171.63]; *P*=0.047).

DISCUSSION

Principal findings

During the first wave of COVID-19 in France, 32.2% of the patients with suspected COVID-19 were classified as "confirmed COVID" cases, 34.9% were classified as "no-COVID"

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cases, and 32.9% were classified as "uncertain COVID" cases. The clinical course was mainly benign, although the hospital admission rate (with no deaths) was 9.8% in the "confirmed COVID" group. In the latter group, the variable "age >70 and/or at least one comorbidity", abnormalities in a lung examination, and two or more systemic symptoms were independently associated with 3-month hospital admission and referral to an emergency department. Moreover, "confirmed COVID-19" patients tended to have more persistent symptoms at 3 months - mainly anosmia and "other persistent symptoms". Fever or feeling feverish, and anosmia were independently associated with the persistence of symptoms.

Strengths and weaknesses of the study

This is one of the few studies to have included solely patients consulting in general practice; most longitudinal studies of COVID-19 patients assessed hospital-based or mixed cohorts. Moreover, our assessment of a prospective multicentre cohort recruited at different primary care health centres means that our results can be more readily extrapolated on the local or regional level. Another study strength was our comparison of "confirmed COVID", "no-COVID" and "uncertain COVID" groups; this provided a more accurate comparison of the initial and subsequent signs and symptoms of COVID-19. The "no COVID" group was particularly relevant for comparing the prevalence of persistent symptoms because it probably comprised patients with other viral diseases.

However, our study had some limitations. Selection bias might have been present because the RT-PCR test was only initially recommended for patients with severity criteria and/or with comorbidities, and for healthcare professionals. This may explain some of the demographic characteristics of confirmed cases. However, this bias was limited by the prescription of serology tests *a posteriori* to patients with compatible symptoms and who had not had an RT-PCR test and to patients with a negative RT-PCR test. We did not include

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under-18 patients and institutionalized patients. The study was limited to the greater Paris region and so might not be representative of the French population as a whole. Moreover, the groups' size might have led to a lack of statistical power. Lastly, only COVID-related hospital admissions were recorded; it would have been useful to collect data on the symptom burden associated with all-cause hospital admissions.

Comparison with other studies

The demographic characteristics of our COVID-19 patients consulting in general practice were similar to those in the literature, particularly with regard to the mean age (43 in our study and in Yordanov et al.'s study [22]), the proportion of caregivers [23-24], and the most prevalent comorbidities (hypertension, and diabetes) [20]. Several studies of ambulatory patients have shown that systemic symptoms (including asthenia, fever, cough, myalgia, and headaches) were frequent [4,25-27]. Anosmia and ageusia were also frequent and appeared later in the course of disease. Some experts consider that the anosmia-ageusia combination is specific for COVID-19 [12]. Digestive tract symptoms were less frequent [4,6,28-30]. Our patients also varied with regard to the signs in the GPs' clinical examination (including abnormalities in a lung examination), as found in systematic reviews [12,31]. In line with our results, most studies of outpatients have found that the course of the disease is benign and that hospital admission is not required [17,22,23]. As found in the present research, literature data have shown that a higher frequency of negative outcomes (hospital admission and death) is associated with older age [32-33] and with comorbidities like cardiovascular disease and diabetes [22,33-34]. In contrast to another study, we did not find an association with male sex [35]. However, no other studies have found that more than two systemic symptoms at the initial GP visit and abnormalities in a lung examination are predictive of an adverse outcome.

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These present findings and the literature data [12,31] highlight the need for a clinical consultation with the GP.

It appears that COVID-19 is a relapsing-remitting disease from which patients recover at different rates [36]. Here, we observed a non-significant trend toward a greater prevalence of persistent symptoms at 3 months in the "confirmed COVID" group (15.7%), vs. the no-COVID group (9.6%). This finding is in line with the results of a UK study in which 13.7% of outpatients had symptoms that persisted for at least 12 weeks [36]. However, the association remained significant in our "confirmed COVID" group for anosmia and "other symptoms" (i.e. deep vein thrombosis, alopecia, palpitations, feeling feverish, and memory impairments), as also reported elsewhere [37]. A recent, large cohort study suggested that self-reported infection was positively associated with persistent physical symptoms, whereas a positive serology test result for SARS-COV-2 was positively associated only with persistent anosmia [13]. Furthermore, it appears that one of the factors determining the presence of persistent symptoms in our COVID patients was the presence of fever during the initial GP visit. This association with fever has only previously been found in one study of elderly people [38] but not in other studies [39].

In our study, a comparison at 3 months showed that some persistent symptoms (asthenia, cough, chest pain, and dyspnoea) were not significantly more frequent in the "confirmed COVID" group - suggesting they were not specific for "long COVID-19". Asthenia and dyspnoea were the two most common persistent symptoms in hospitalized and non-hospitalized patients [40]. However, we observed asthenia and dyspnoea respectively in around only 4% and 3% of our "confirmed COVID" patients, and with much the same frequency as in no COVID-19 patients (4.5% and 4.5%, respectively). Outpatient studies with a control group found the presence of persistent symptoms up to 10 [41] and 12 months [42] after mild COVID-19, with miscellaneous symptoms: asthenia, headaches, smell and

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taste disorders, dyspnoea, memory disorders, insomnia, and difficulty concentrating [41-42]. The French health authorities also included neurological, cardiothoracic and sensory disorders in the list of persistent symptoms [43].

The results of these "long COVID-19" studies are relatively disparate and appear to show that this entity is non-specific because of the multisymptomatic, fluctuating nature of the clinical manifestations [43].

Implications for clinicians and policymakers

It is important to provide GPs with primary-care-specific data that enable them to optimize patient management. GPs have an essential role in combating the pandemic [44] and diagnose most patients with COVID-19 [2]. Identifying prognostic factors and examining patients for clinical abnormalities could help to detect patients at risk, set up follow-up procedures, and anticipate possible worsening [2,45]. These strategies might be needed in France, with a view to enabling primary care to withstand future health emergencies and pandemics, as has been mentioned in Australia, New Zealand, Canada, the Netherlands, the UK, and the US [46]. The trend towards more frequent persistent symptoms in patients with COVID-19 (more specifically, anosmia and "other symptoms") suggests that follow-up by the GP should take account of the disease's impact on quality of life, overall health and life context via a patient-centred approach [47].

Unanswered questions and future research

Our findings (notably concerning persistent symptoms) need to be confirmed in the longer term and in other patient populations (e.g. institutionalized people, children, and adolescents). Our study was partly based on electronic medical records and showed that

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primary care can provide important public health data. This work could be expanded with patient surveys and GP interviews, so as to combine real-time data on patients' symptoms and adverse outcomes with patient responses to public health messaging and information on the GPs' adaptive coping mechanisms [46].

CONCLUSIONS

Cases of COVID-19 seen in primary care have an essentially benign course. However, age >70 and/or at least one comorbidity, abnormalities in a lung examination, and a higher number of systemic symptoms were associated with hospital admission and referral to an emergency department. Our results reinforce the need for a face-to-face medical consultation by the GP to identify patients at risk of severe disease. Almost 1 in 6 COVID-19 patients had persistent symptoms at 3 months - emphasizing the need for an overall, patient-centred approach. This frequency of persistent symptoms tended to be higher in COVID-19 patients than in no-COVID-19 cases. Anosmia and a group of rarer symptoms were more prevalent in the "confirmed COVID" group. Asthenia, chest pain, cough, and dyspnoea were also present in the other groups and might not be specific for a possible "long COVID-19". Our findings in primary care need to be confirmed in prospective studies with a longer follow-up period.

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Supplementary and raw data: The characteristics of the participating GPs and their practices are presented in Online supplement 1. Table S1.

REFERENCES

[1] Saint-Lary O, Gautier S, Le Breton J, Gilberg S, Frappé P, et al. How GPs adapted their practices and organisations at the beginning of COVID-19 outbreak: a French national observational survey. BMJ Open. 2020;10:e042119. doi: 10.1136/bmjopen-2020-042119

[2] Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. BMJ. 2020 Mar 25;368:m1182. doi: 10.1136/bmj.m1182.

[3] Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ. 2020 May 29;369:m1996. doi: 10.1136/bmj.m1996.

[4] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020 May 22;369:m1985. doi: 10.1136/bmj.m1985.

[5] Tostmann A, Bradley J, Bousema T, Yiek WK, Holwerda M, Bleeker-Rovers C, et al. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, March 2020. Euro Surveill. 2020 Apr;25(16):2000508. doi: 10.2807/1560-7917.ES.2020.25.16.2000508.

For peer review only

[6] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020 Jul;75(7):1730-1741. doi: 10.1111/all.14238. Epub 2020 Feb 27.

[7] Lechien JR, Chiesa-Estomba C, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020 Aug;277(8):2251-2261. doi: 10.1007/s00405-020-05965-1. Epub 2020 Apr 6.

[8] Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 6;397(10270):220-232. doi: 10.1016/S0140-6736(20)32656-8. Epub 2021 Jan 8.

[9] Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020 Sep;288(3):335-344. doi: 10.1111/joim.13089. Epub 2020 Jun 17.

[10] Villerabel C, Makinson A, Jaussent A, Picot M, Nègre-Pagès L, Morquin D, et al. Dépistage de la COVID-19 : valeurs diagnostiques d'une anosmie rapportée ou objectivée par un test clinique. Med Mal Infect. 2020 Sep; 50(6): S78.

[11] Zayet S, Klopfenstein T, Royer P, Toko L, Kadiane-Oussou N, Gendrin V. Sensibilité, spécificité et valeurs prédictives des signes fonctionnels de l'infection par SARS-CoV-2. Med Maladies Infect. 2020 Sep;50(6) :S77.

[12] Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MMG, et al. Cochrane COVID-19 Diagnostic Test Accuracy Group. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database of

For peer review only

Systematic Reviews 2021, Issue 2. Art. No.: CD013665. DOI: 10.1002/14651858.CD013665.pub2.

[13] Matta J, Wiernik E, Robineau O, Carrat F, Touvier M, Severi G, et al. Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic. JAMA Intern. Med. JAMA Intern Med . 2021 Nov 8;e216454. doi: 10.1001/jamainternmed.2021.6454.

[14] Nehme M, Braillard O, Chappuis F, Courvoisier DS, Guessous I; CoviCare Study Team. Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in an Outpatient Setting. Ann Intern Med. 2021 Sep;174(9):1252-1260. doi:10.7326/M21-0878. Epub 2021 Jul 6.

[15] Cirulli ET, Schiabor Barrett KM, Riffle S, Bolze A, Neveux I, Dabe S, et al. (2020) Long-term COVID-19 symptoms in a large unselected population. medRxiv: 2020100720208702.

[16] French High Council of Public Health. Haut Conseil de la Santé Publique, 2020. Available: https://solidarites-sante.gouv.fr/IMG/pdf/hcsp_sars-cov2-priorisationtestsdiagnostiques-2020-03-11-2.pdf

[17] French High Autority for Health. Réponses rapides dans le cadre de la COVID-19. Prise en charge de premier recours des patients atteints de Covid-19. Haute Autorité de Santé, 2020 Available: https://www.has-sante.fr/upload/docs/application/pdf/2022-02/reco453_rr_covid_19_premier_recours_20220216_mel.pdf

[18] French High Autority for Health. Premières indications pour les tests sérologiques du COVID-19. Haute Autorité de Santé, 2020. Available: https://www.has-sante.fr/jcms/p_3182370/fr/premieres-indications-pour-les-tests-serologiques-du-covid-19

For peer review only

[19] French Society of Radiology. Epidémie de COVID-19 : POINT SUR L'IMAGERIE. Société Française de Radiologie, 2020. Available: https://ebulletin.radiologie.fr/actualites-covid-19/epidemie-covid-19-point-limagerie

[20] French High Autority for Health. Réponses rapides dans le cadre de la COVID-19 - Place du scanner thoracique. Haute Autorité de Santé, 2020. Available: https://www.has-sante.fr/upload/docs/application/pdf/2020-04/reponse_rapide_codid-19_indication_tdm_mel2.pdf

[21] Hox JJ, Moerbeek M, van de Schoot R. Multilevel Analysis, techniques and applications. Third Edition, 2018. Routledge, New York.

[22] Yordanov Y, Dinh A, Bleibtreu A, Mensch A, Lescure FX, Debuc E, et al.. Clinical characteristics and factors associated with hospital admission or death in 43 103 adult outpatients with coronavirus disease 2019 managed with the Covidom telesurveillance solution: a prospective cohort study. Clin Microbiol Infect. 2021 Aug;27(8):1158-1166. doi: 10.1016/j.cmi.2021.04.010. Epub 2021 Apr 27.

[23] Wu Z, McGoogan MJ. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-1242. doi: 10.1001/jama.2020.2648.

[24] Riccardo F, Ajelli M, Andrianou XD, Bella A, Del Manso M, Fabiani M, et al. Epidemiological characteristics of COVID-19 cases and estimates of the reproductive numbers 1 month into the epidemic, Italy, 28 January to 31 March 2020. Euro Surveill. 2020 Dec;25(49):2000790. doi: 10.2807/1560-7917.ES.2020.25.49.2000790.

[25] Lapostolle F, Schneider E, Vianu I, Dollet G, Roche B, Berdah J, et al. Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-

For peer review

call study. Intern Emerg Med. 2020 Aug;15(5):813-817. doi: 10.1007/s11739-020-02379-z. Epub 2020 May 30.

[26] Khan M, Khan H, Khan S, Nawaz M. Epidemiological and clinical characteristics of coronavirus disease (COVID-19) cases at a screening clinic during the early outbreak period: a single-centre study. J Med Microbiol. 2020 Aug;69(8):1114-1123. doi:10.1099/jmm.0.001231.

[27] Ayaz CM, Dizman GT, Metan G, Alp A, Unal S. Out-patient management of patients with COVID-19 on home isolation. Infez Med. 2020 Sep 1;28(3):351-356.

[28] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24.

[29] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20. DOI: 10.1056/NEJMoa2002032

[30] Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer S, et al. High Prevalence of Concurrent Gastrointestinal Manifestations in Patients With Severe Acute Respiratory Syndrome Coronavirus 2: Early Experience from California. Gastroenterology. 2020 Aug;159(2):775-777. doi: 10.1053/j.gastro.2020.04.008. Epub 2020 Apr 10.

[31] Izcovich A, Ragusa MA, Tortosa F, Marzio MAL, Agnoletti C, Bengolea A, et al. Correction: Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLOS ONE 2022;17(5): e0269291. https://doi.org/10.1371/journal.pone.0269291

[32] Dres M, Hajage D, Lebbah S, Kimmoun A, Pham T, Béduneau G, et al. Characteristics, management, and prognosis of elderly patients with COVID-19 admitted in the ICU during the first wave: insights from the COVID-ICU study : Prognosis of COVID-19 elderly

For peer review only

critically ill patients in the ICU. Ann Intensive Care. 2021 May 14;11(1):77. doi: 10.1186/s13613-021-00861-1.

[33] Tenreiro P, Ramalho A, Santos P. COVID-19 patients followed in Portuguese Primary Care: a retrospective cohort study based on the national case series. Fam Pract. 2022 Jan 19;39(1):52-58. doi: 10.1093/fampra/cmab098.

[34] Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira R, Weill A, et al. Maladies chroniques, états de santé et risque d'hospitalisation et de décès hospitalier pour COVID-19: analyse comparative de données des deux vagues épidémiques de 2020 en France à partir d'une cohorte de 67 millions de personnes. 2021. Available: https://www.epi-phare.fr/app/uploads/2021/07/epi-phare_risques_hospitalisations_deces_covid19_20210721.pdf

[35] Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020 Dec 9;11(1):6317. doi: 10.1038/s41467-020-19741-6.

[36] Office for national Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 April 2021. 2021. Available : https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1april2021

[37] French High Council of Public Health. Avis relatif aux symptômes cliniques persistants au décours d'un COVID-19. Haut Conseil de la Santé Publique, 2021. Available: https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1037

For peer review only

[38] Sudre CH, Murray B, Varsaysky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long-COVID. Nat Med. 2021 Jun;27(6):1116. doi: 10.1038/s41591-021-01361-2.

[39] Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. Lancet Reg Health Eur. 2021 Jul;6:100122. doi: 10.1016/j.lanepe.2021.100122. Epub 2021 May 18.

[40] Rajan S, Khunti K, Alwan N, Steves C, Greenhalgh T, MacDermott N, et al. In the wake of the pandemic: Preparing for Long COVID. 2021. Available: https://apps.who.int/iris/bitstream/handle/10665/339629/Policy-brief-39-1997-8073-eng.pdf

[41] Desgranges F, Tadini E, Munting A, Regina J, Filippidis P, Viala B, et al. Post-COVID-19 Syndrome in Outpatients: a Cohort Study. J Gen Intern Med. 2022 Jun;37(8):1943-1952. doi: 10.1007/s11606-021-07242-1. Epub 2022 Mar 22. PMID: 35319081; PMCID: PMC8939498.

[42] Nehme M, Braillard O, Chappuis F, Courvoisier DS, Kaiser L, Soccal PM, et al. One-year persistent symptoms and functional impairment in SARS-CoV-2 positive and negative individuals. J Intern Med. 2022 Jul;292(1):103-115. doi: 10.1111/joim.13482. Epub 2022 Mar 31. PMID: 35555926; PMCID: PMC9115262.

[43] French High Autority for Health. Symptômes prolongés suite à une Covid-19 de l'adulte - Diagnostic et prise en charge. Haute Autorité de Santé, 2021. Available: https://www.has-sante.fr/jcms/p_3237041/fr/symptomes-prolonges-suite-a-une-covid-19-de-l-adulte-diagnostic-et-prise-en-charge

For peer review only

[44] Sarti TD, Lazarini WS, Fontenelle LF, et al. What is the role of primary health care in the COVID-19 pandemic? Epidemiol Serv Saude 2020;29:e2020166.

[45] Prado NMBL, Biscarde DGDS, Pinto Junior EP, Santos HLPCD, Mota SEC, Menezes ELC, et al. Primary care-based health surveillance actions in response to the COVID-19 pandemic: contributions to the debate Cien Saude Colet. 2021 Jul;26(7):2843-2857. doi: 10.1590/1413-81232021267.00582021. Epub 2021 Mar 29.

[46] Huston P, Campbell J, Russell G, Goodyear-Smith F, Phillips RL Jr, van Weel C, Hogg W. COVID-19 and primary care in six countries. BJGP Open. 2020 Oct 27;4(4):bjgpopen20X101128. doi: 10.3399/bjgpopen20X101128. Print 2020 Oct.

[47] Stewart M. Patient-Centred Medicine: Transforming the Clinical Method. 3rd ed. London, CRC Press 2019; 442p.

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Figure 1. Study flow diagram

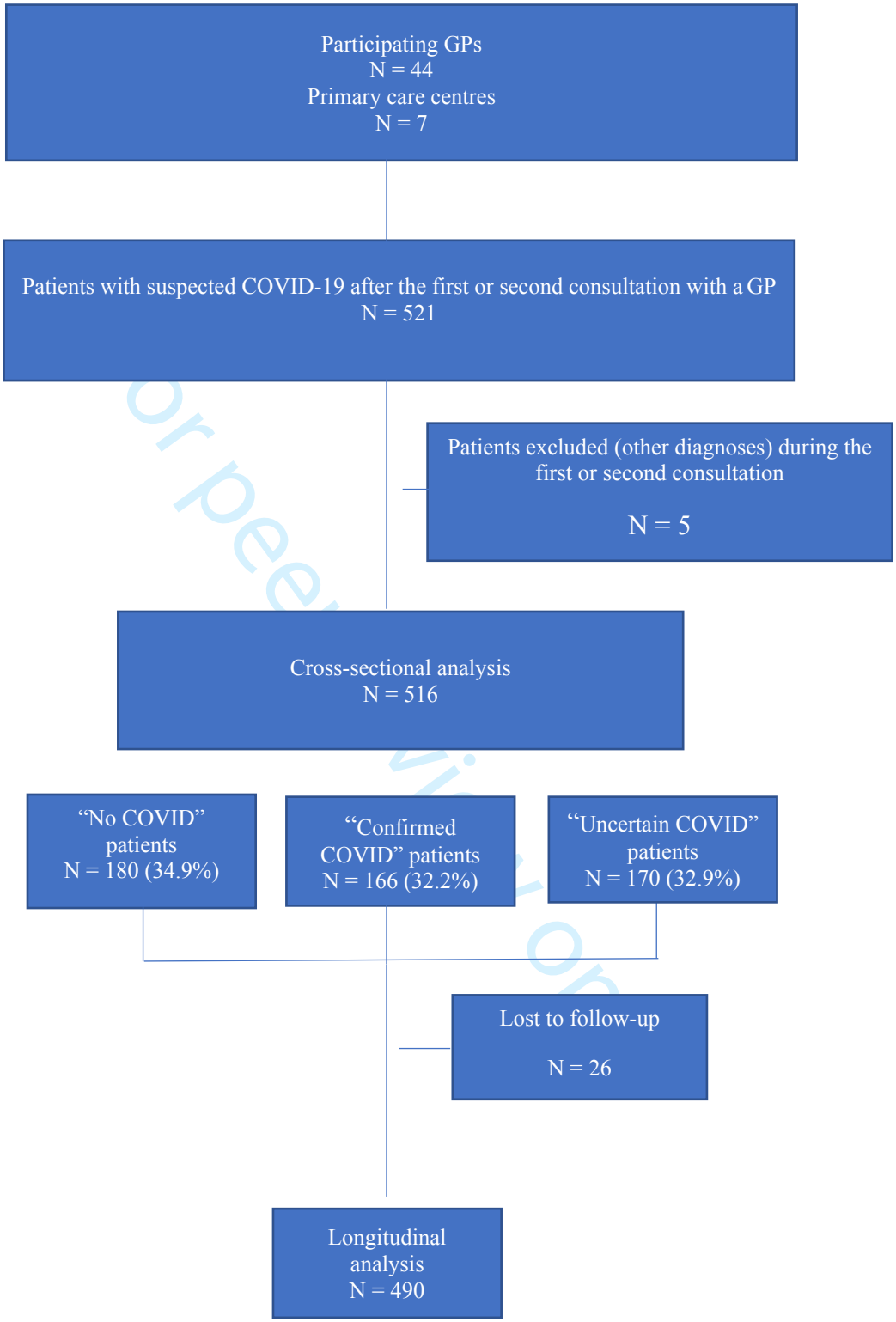

Table 1. Characteristics of the study population and univariate comparison of the three patient groups (N=516)

	Total n=516	No COVID n=180 (34.9%)	Confirmed COVID n=166 (32.2%)	Uncertain COVID n=170 (32.9%)	p[a]	Confirmed COVID vs no-COVID OR[95%CI]	p[b]	Confirmed COVID vs uncertain COVID OR [95%CI]	p[b]
Age (years) (median, IQR)	43 [33-56]	45 [35-56.5]	49 [39-59]	36 [29-49]	<0.001	1.02 [1.01-1.03]	0,027	1.04 [1.03-1.06]	<0.001
Male sex	195 (37.8)	61 (33.9)	58 (34.9)	76 (44.7)	0,074	0.99 [0.63-1.56]	0,957	0.58 [0.36-0.93]	0,046
Caregivers (n=463/165/149/149)	58 (12.5)	17 (10.3)	31 (20.8)	10 (6.7)	0,001	2.70 [1.39-5.24]	0,003	5.58 [2.50-12.46]	<0.001
Contact with confirmed positive case (n=290/96/98/96)					<0.001		0,006		<0.001
No	130 (44.8)	48 (50.0)	30 (30.6)	52 (54.2)		1 (ref)		1 (ref)	
Yes	67 (23.1)	19 (19.8)	36 (36.7)	12 (12.5)		3.48 [1.62-7.51]		8.77 [3.59-21.46]	
Uncertain	93 (32.1)	29 (30.2)	32 (32.7)	32 (33.3)		1.95 [0.95-4.01]		2.59 [1.22-5.51]	
Smoking (n=159/62/52/45)	64 (40.3)	28 (45.2)	16 (30.8)	20 (44.4)	0,235				
At least one comorbidity (n=509/178/164/167)	207 (40.7)	85 (47.8)	77 (47.0)	45 (27.0)	<0.001	0.84 [0.52-1.31]	0,416	1.67 [1.01-2.79]	0,092
Dyslipidaemia (n=509/178/164/167)	16 (3.1)	8 (4.5)	7 (4.3)	1 (0.6)	0,071	0.73 [0.24-2.18]	0,570	3.11 [0.36-27.18]	0,57
Obesity (n=173/59/59/55)	67 (38.7)	25 (42.4)	23 (39.0)	19 (34.6)	0,692				
Hypertension (n=509/178/164/167)	70 (13.8)	25 (14.0)	29 (17.7)	16 (9.6.)	0,100	1.05 [0.54-2.03]	0,882	0.88 [0.42-1.88]	0,882
Diabetes (n=509/178/164/167)	31 (6.1)	18 (10.1)	7 (4.3)	6 (3.6)	0,020	0.28 [0.11-0.73]	0,018	0.62 [0.19-2.00]	0,423
Cardiovascular disease (n=509/178/164/167)	33 (6.5)	9 (5.1)	16 (9.8)	8 (4.8)	0,117	1.81 [0.73-4.45]	0,398	0.94 [0.36-2.48]	0,903
Asthma (n=509/178/164/167)	52 (10.2)	19 (10.7)	15 (9.2)	18 (10.8)	0,859				
COPD (n=509/178/164/167)	9 (1.8)	6 (3.4)	0 (0)	3 (1.8)					
Venous thromboembolism (n=509/178/164/167)	7 (1.4)	4 (2.3)	1 (0.6)	2 (1.2)					
Inflammatory rheumatic disease (n=509/178/164/167)	9 (1.8)	4 (2.3)	2 (1.2)	3 (1.8)					
Cancers (n=509/178/164/167)	13 (2.6)	8 (4.5)	4 (2.4)	1 (0.6)	0,059	0.48 [0.14-1.69]	0,407	2.61 [0.27-25.37]	0,407
Autoimmune diseases (MS, UC, Crohn's, SLE, sarcoidosis, Basedow...) (n=509/178/164/167)	15 (3.0)	10 (5.6)	4 (2.4)	1 (0.6)	0,015	0.33 [0.10-1.13]	0,154	3.03 [0.32-28.38]	0,332
Age > 70 and/or presence of at least one comorbidity (n=509/178/164/167)	210 (41.2)	85 (47.8)	78 (47.6)	47 (28.1)	<0.001	1.03 [0.67-1.59]	0,899	2.33 [1.45-3.74]	<0.001
Mode of consultation (n=515/179/166/170)					0,526				
Presential	345 (67.0)	125 (69.8)	114 (68.7)	106 (62.4)					

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Teleconsultation	157 (30.5)	50 (27.9)	48 (28.9)	59 (34.7)					
Phone	10 (1.9)	4 (2.3)	2 (1.2)	4 (2.3)					
Home visit	3 (0.6)	0 (0)	2 (1.2)	1 (0.6)					
Symptoms at the initial consultation									
Fever or feeling feverish (n=469/158/151/160)	200 (42.6)	68 (43.0)	81 (53.6)	51 (31.9)	0,001	1.58 [0.99-2.53]	0,058	2.15 [1.31-3.52]	0,004
Asthenia (n=184/74/61/49)	145 (78.8)	56 (75.7)	50 (82.0)	39 (79.6)	0,665				
Muscle ache (n=370/117/123/130)	219 (59.2)	67 (57.3)	85 (69.1)	67 (51.5)	0,015	1.63 [0.95-2.80]	0,074	1.91 [1.11-3.29]	0,04
Headache (n=358/121/108/129)	216 (60.3)	76 (62.8)	59 (54.6)	81 (62.8)	0,349				
Rhinorrhoea (n=366/126/109/131)	194 (53.0)	75 (59.5)	56 (51.4)	63 (48.1)	0,171				
Cough (n=471/163/149/159)	366 (77.7)	127 (77.9)	119 (79.9)	120 (75.5)	0,649				
Expectorations (n=265/80/80/105)	61 (23.0)	17 (21.3)	18 (22.5)	26 (24.8)	0,846				
Chest pain (n=325/107/103/115)	80 (24.6)	39 (36.5)	19 (18.5)	22 (19.1)	0,002	0.40 [0.21-0.77]	0,012	0.97 [0.48-1.98]	0,94
Dyspnoea at rest and/or on exertion (n=370/131/116/123)	128 (34.6)	56 (42.8)	35 (30.2)	37 (30.1)	0,051	0.56 [0.32-0.96]	0,07	1.09 [0.61-1.96]	0,77
Sore throat (n=351/122/102/127)	177 (50.4)	73 (59.8)	44 (43.1)	60 (47.2)	0,030	0.50 [0.29-0.88]	0,032	0.91 [0.53-1.58]	0,746
Anosmia (n=317/109/100/108)	74 (23.3)	11 (10.1)	42 (42.0)	21 (19.4)	<0.001	7.11 [3.30-15.29]	<0.001	3.74 [1.91-7.31]	<0.001
Agueusia (n=282/89/94/99)	75 (26.6)	13 (14.6)	42 (44.7)	20 (20.2)	<0.001	4.79 [2.31-9.93]	<0.001	3.38 [1.73-6.59]	<0.001
Nausea and/or vomiting (n=343/120/100/123)	50 (14.6)	19 (15.8)	15 (15.0)	16 (13.0)	0,815				
Diarrhoea (n=360/127/110/123)	84 (23.3)	33 (26.0)	32 (29.1)	19 (15.5)	0,033	1.21 [0.68-2.17]	0,513	2.58 [1.31-5.07]	0,012
Abdominal pain (n=143/57/44/42)	19 (13.3)	7 (12.3)	7 (15.9)	5 (11.9)	0,826				
Number of symptoms (tertile; n=511/179/163/169)					0,528				
≤3	181 (35.4)	68 (38.0)	49 (30.1)	64 (37.9)					
4-5	184 (36.0)	62 (34.6)	62 (38.0)	60 (35.5)					
>5	146 (28.6)	49 (27.4)	52 (31.9)	45 (26.6)					
Number of systemic symptoms (tertile; n=511/179/163/169)					0,020				
≤1	216 (42.3)	82 (45.8)	56 (34.3)	78 (46.2)		1 (ref)	0,100	1 (ref)	0,072
2	142 (27.8)	40 (22.4)	49 (30.1)	53 (31.4)		1.80 [1.04-3.11]		1.19 [0.69-2.05]	
>2	153 (29.9)	57 (31.8)	58 (35.6)	38 (22.5)		1.42 [0.85-2.37]		1.83 [1.04-3.22]	
Number of ENT symptoms (tertile; n=511/179/163/169)					0,277				
0	182 (35.6)	62 (34.6)	55 (33.7)	65 (38.5)					
1	188 (36.8)	75 (41.9)	55 (33.7)	58 (34.3)					
>1	141 (27.6)	42 (23.5)	53 (32.6)	46 (27.2)					

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Clinical examination								
Temperature>38°C					0,012		0,343	<0.001
No	325 (63.0)	110 (61.1)	92 (55.4)	123 (72.4)		1 (ref)		1 (ref)
Yes	39 (7.6)	15 (8.3)	18 (10.8)	6 (3.5)		1.52 [0.71-3.24]		4.09 [1.48-11.30]
Uninformed	152 (29.4)	55 (30.6)	56 (33.7)	41 (24.1)		1.35 [0.83-2.20]		2.30 [1.35-3.91]
Respiratory rate (cpm) (n=101/41/38/22)	18 [16-20]	18 [16-20]	20 [17-20]	18 [16-20]	0,387			
SaO2 (%) (n=272/91/96/85)	98 [97-99]	98 [97-99]	98 [97-99]	98 [97-99]	0,153			
Abnormalities in a lung examination					0,585			
No	270 (52.3)	94 (52.2)	90 (54.2)	86 (50.6)				
Yes	48 (9.3)	20 (11.1)	16 (9.7)	12 (7.1)				
Uninformed	198 (38.4)	66 (36.7)	60 (36.1)	72 (42.3)				

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

a The p-values were obtained in a chi-squared test or Fisher's exact test for qualitative variables and the Kruskal Wallis test for quantitative variables

b Age-adjusted multilevel multinomial logistic regression; p-values of paire-wise comparisons were corrected by the False discovery rate method

COPD, Chronic obstructive pulmonary disease; MS, Multiple Sclerosis; UC, ulcerative colitis; SLE systemic lupus erythematosus; ENT, Ear Nose Throat; OR: odds ratio; CI:confidence interval

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Table 2. Comparison of 3-month persistent symptoms between Covid vs no Covid groups (N=346)

		Main analysis				Sensitivity analysis	
	No COVID n=180	**Confirmed COVID n=166**	**p[a]**	**Confirmed COVID vs no-COVID OR [95%CI]**	**p[b]**	**Confirmed COVID vs no-COVID OR [95%CI] (N=195 vs 180)**	**p[b]**
Any persistent symptom combined (n=177/159//182)	17 (9.6)	25 (15.7)	0,090	1.66 [0.86-3.23]	0,133	1.67 [0.88-3.19]	0,118
Asthenia (n=177/159//182)	8 (4.5)	6 (3.8)	0,733				
Cough (n=177/159//182)	3 (1.7)	4 (2.5)	0,712				
Dyspnoea (n=177/159//182)	8 (4.5)	5 (3.1)	0,514				
Chest pain (n=177/159//182)	3 (1.7)	3 (1.9)	1				
Anosmia (n=177/159//182)	1 (0.6)	7 (4.4)	0,029	8.51 [1.03-70.43]	0,047	8.36 [1.03-67.68]	0,047
Agueusia (n=177/159//182)	3 (1.7)	4 (2.5)	0,712				
Other symptoms (n=177/159//182)	1 (0.6)	7 (4.4)	0,029	7.02 [0.84-58.29]	0,071	7.62 [0.94-61.87]	0,058
deep vein thrombosis	0 (0)	1 (14.3)					
alopecia	0 (0)	1 (14.3)					
myalgia	0 (0)	1 (14.3)					
palpitations	0 (0)	1 (14.3)					
pruritus, rash	1 (100)	0 (0)					
feeling feverish	0 (0)	2 (28.6)					
memory impairments	0 (0)	1 (14.3)					

Data are quoted as the n (%)

a The p-values were obtained in a chi-squared test or Fisher's exact test

b Age adjusted multilevel logistic regression

OR: odds ratio; CI:confidence interval

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Table 3. Multilevel univariate analysis of factors associated with 3-month persistent symptoms among patients with confirmed COVID-19 (n=159)

	3-month persistent symptoms			Univariate analysis		Multivariate analysis (final model)	
	No, n=134 (84.3%)	Yes, n=25 (15.7%)	p[a]	OR [95%CI]	p[b]	OR [95%CI]	p[b]
Age (years)	48 [39-58]	51 [41-59]	0,509				
Male sex	49 (36.6)	6 (24.0)	0,225				
Caregivers (n=120/22)	24 (20.0)	5 (22.7)	0,776				
Smoking (n=38/10)	14 (36.8)	2 (20.0)	0,460				
At least one comorbidity (n=133/25)	60 (45.1)	13 (52.0)	0,526				
Dyslipidaemia (n=133/25)	5 (3.8)	2 (8.0)	0,306				
Obesity (n=47/9)	18 (38.3)	5 (55.6)	0,464				
Hypertension (n=133/25)	23 (17.3)	3 (12.0)	0,769				
Diabetes (n=133/25)	6 (4.5)	1 (4.0)	1				
Cardiovascular disease (n=133/25)	11 (8.3)	3 (12.0)	0,466				
Asthma (n=133/25)	11 (8.3)	4 (16.0)	0,261				
Age > 70 and/or presence of at least one comorbidity (n=133/25)	61 (45.9)	13 (52.0)	0,573				
Symptoms at the initial consultation							
Fever or feeling feverish (n=122/22)	59 (48.4)	17 (77.3)	0,012	3.63 [1.26-10.46]	0,017	6.93 [1.62-29.53]	0,009
Asthenia (n=51/7)	42 (82.4)	7 (100)	0,581				
Muscle ache (n=99/19)	68 (68.7)	16 (84.2)	0,171				
Headache (n=88/16)	49 (55.7)	10 (62.5)	0,613				
Rhinorrhoea (n=86/17)	42 (48.8)	11 (64.7)	0,232				
Cough (n=121/23)	93 (76.9)	21 (91.3)	0,163				
Expectorations (n=62/15)	15 (24.2)	3 (20.0)	1				
Chest pain (n=80/17)	15 (18.8)	4 (23.5)	0,737				
Dyspnoea at rest and/or on exertion (n=96/16)	29 (30.2)	5 (31.3)	1				
Sore throat (n=82/16)	36 (43.9)	6 (37.5)	0,636				
Anosmia (n=81/15)	32 (39.5)	10 (66.7)	0,051	3.06 [0.96-9.797]	0,059	4.79 [1.30-17.66]	0,019
Agueusia (n=73/17)	30 (41.1)	11 (64.7)	0,078	2.63 [0.88-7.88]	0,085		
Nausea and/or vomiting (n=77/17)	12 (15.6)	1 (5.9)	0,451				
Diarrhoea (n=86/18)	25 (29.1)	5 (27.8)	0,912				
Abdominal pain (n=31/8)	6 (19.4)	0 (0)	0,313				
Number of symptoms (tertile; n=132/25)			0,108		0,130		
≤4	72 (54.5)	8 (32.0)		1 (ref)			
5	21 (15.9)	6 (24.0)		2.57 [0.80-8.24]			
>5	39 (29.6)	11 (44.0)		2.54 [0.94-6.84]			
Number of systemic symptoms (tertile; n=132/25)			0,355				
≤1	45 (34.1)	7 (28.0)					

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2-3	70 (53.0)	12 (48.0)	
>3	17 (12.9)	6 (24.0)	
Number of ENT symptoms (tertile; n=132/25)			0,189
0	47 (35.6)	6 (24.0)	
1	46 (34.8)	7 (28.0)	
>1	39 (29.6)	12 (48.0)	
Clinical examination			
Temperature>38°C			0,375
No	77 (57.5)	11 (44.0)	
Yes	14 (10.4)	4 (16.0)	
Uninformed	43 (32.1)	10 (40.0)	
Respiratory rate (cpm) (n=27/8)	20 [18-20]	19 [15-20]	0,434
SaO2 (%) (n=80/12)	98 [97-99]	98 [97-98.5]	0,624
Abnormalities in a lung examination			0,261
No	74 (55.2)	10 (40.0)	
Yes	14 (10.5)	2 (8.0)	
Uninformed	46 (34.3)	13 (52.0)	

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

a The p-values were obtained in the chi-squared test or the Fisher's exact test for qualitative variables, and the Mann-Whitney test for quantitative variables

b Multilevel logistic regression

ENT, Ear Nose Throat; OR: odds ratio; CI:confidence interval

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Table 4. Multilevel univariate analysis of factors associated with 3-month composite criterion among patients with confirmed COVID-19 (n=165)

				Univariate analysis		Multivariate analysis (final model)	
	No composite criterion n=147 (89.1%)	Composite criterion n=18 (10.9%)	p[a]	OR [95%CI]	p[b]	OR [95%CI]	p[b]
Age (years)	47 [37-58]	62.5 [50-78]	<0.001	1.08 [1.03-1.13]	0,003		
Male sex	49 (33.3)	9 (50.0)	0,162				
Caregivers (n=133/15)	29 (21.8)	1 (6.7)	0,307				
Smoking (n=46/6)	14 (30.4)	2 (33.3)	1				
At least one comorbidity (n=145/18)	63 (43.5)	13 (72.2)	0,021	4.04 [1.16-14.00]	0,028		
Dyslipidaemia (n=145/18)	4 (2.8)	3 (16.7)	0,030	8.82 [1.28-60.64]	0,027		
Obesity (n=53/5)	22 (41.5)	1 (20.0)	0,639				
Hypertension (n=145/18)	21 (14.5)	7 (38.9)	0,017	3.71 [1.19-11.53]	0,023		
Diabetes (n=145/18)	4 (2.8)	3 (16.7)	0,030	8.23 [1.32-51.34]	0,024		
Cardiovascular disease (n=145/18)	10 (6.9)	6 (33.3)	0,003	7.51 [1.95-28.93]	0,003		
Asthma (n=145/18)	13 (9.0)	2 (11.1)	0,673				
Age > 70 and/or presence of at least one comorbidity (n=145/18)	64 (44.1)	13 (72.2)	0,024	3.92 [1.13-13.60]	0,032	6.53 [1.13-37.84]	0,036
Symptoms at the initial consultation							
Fever or feeling feverish (n=133/17)	66 (49.6)	14 (82.4)	0,011	4.68 [1.24-17.79]	0,023		
Asthenia (n=48/12)	37 (77.1)	12 (100)	0,099	-	-	-	-
Muscle ache (n=111/11)	75 (67.6)	10 (90.9)	0,170				
Headache (n=99/8)	55 (55.6)	4 (50.0)	1				
Rhinorrhoea (n=99/9)	51 (51.5)	4 (44.4)	0,740				
Cough (n=133/15)	108 (81.2)	10 (66.7)	0,188				
Expectorations (n=74/6)	15 (20.3)	3 (50.0)	0,124	4.73 [0.48-47.01]	0,184		
Chest pain (n=92/10)	18 (19.6)	1 (10.0)	0,683				
Dyspnoea at rest and/or on exertion (n=103/13)	30 (29.1)	5 (38.5)	0,528				
Sore throat (n=93/9)	41 (44.1)	3 (33.3)	0,728				
Anosmia (n=90/10)	39 (43.3)	3 (30.0)	0,513				
Agueusia (n=86/8)	39 (45.4)	3 (37.5)	0,728				
Nausea and/or vomiting (n=90/9)	13 (14.4)	1 (11.1)	1				
Diarrhoea (n=100/9)	28 (28.0)	3 (33.3)	0,712				
Abdominal pain (n=39/5)	6 (15.4)	1 (20.0)	1				
Number of symptoms (tertile; n=145/17)			0,379				
≤4	76 (52.4)	7 (41.2)					
5	26 (17.9)	2 (11.8)					
>5	43 (26.7)	8 (47.0)					
Number of systemic symptoms (median; n=145/17)			0,009		0,022		0,011
≤1	55 (37.9)	1 (5.9)		1 (ref)		1 (ref)	
≥2	90 (62.1)	16 (94.1)		13.82 [1.45-131.88]		38.61 [2.30-647.40]	

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Number of ENT symptoms (tertile; n=145/17)			0,378				
0	48 (33.1)	7 (41.2)					
1	47 (32.4)	7 (41.2)					
>1	50 (34.5)	3 (17.6)					
Clinical examination							
Temperature>38°C			0,051		0,082		
No	84 (57.2)	7 (38.9)		1 (ref)			
Yes	13 (8.8)	5 (27.8)		5.16 [1.20-22.30]			
Uninformed	50 (34.0)	6 (33.3)		1.27 [0.36-4.49]			
Respiratory rate (cpm) (n=32/5)	18.5 [16-20]	21 [20-24]	0,058	1.14 [0.97-1.34]	0,103		
SaO2 (%) (n=85/10)	98 [97-99]	94.5 [90-98]	0,002	0.28 [0.09-0.91]	0,034		
Abnormalities in a lung examination			0,126		0,179		0,057
No	82 (55.8)	7 (38.9)		1 (ref)		1 (ref)	
Yes	12 (8.2)	4 (22.2)		4.33 [0.92-20.37]		15.39 [1.61-146.77]	
Uninformed	53 (36.0)	7 (38.9)		1.55 [0.47-5.17]		2.63 [0.52-13.34]	

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

a The p-values were obtained in the chi-squared test or the Fisher's exact test for qualitative variables, and the Mann-Whitney test for quantitative variables

b Multilevel logistic regression

ENT, Ear Nose Throat; OR: odds ratio; CI:confidence interval

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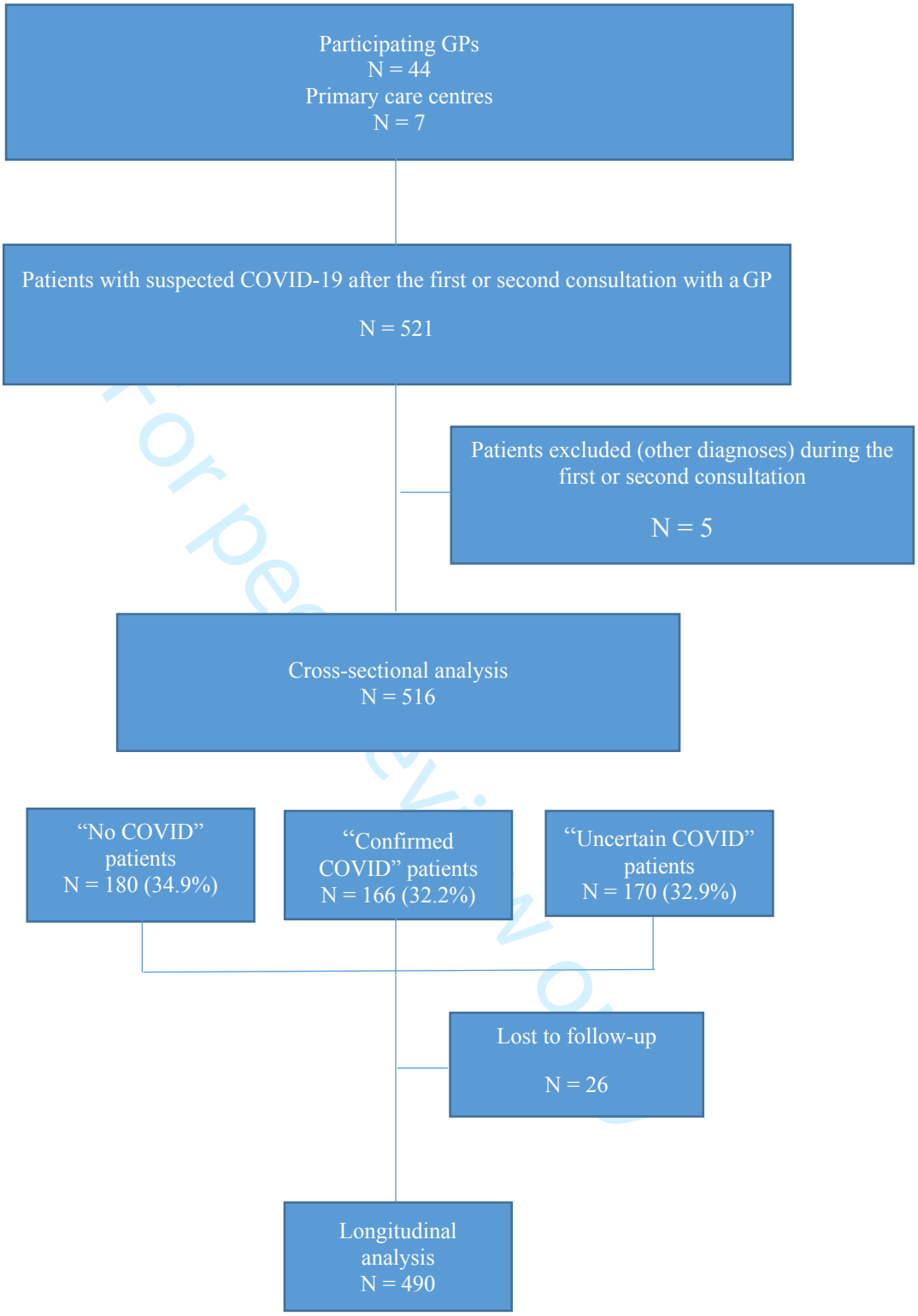
Figure 1. Study flow diagram



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Online supplement 1. Table S1. Characteristics of the participating GPs and their practices

	Total n=44
Number of patients included per GP (median [IQR])	10.5 [3-24.5]
Number of participating GPs per centre	
MPCC Fontainebleau	6 (13.6)
CHC La Courneuve	6 (13.6)
MPCC Coulommiers	9 (20.5)
MPCC Epinay-sous-Sénart	5 (11.4)
MPCC Saint-Maur-des-Faussées	4 (9.1)
MPCC Torcy	10 (22.7)
MPCC Nemours	4 (9.1)
Age of GP (y) (median [IQR]) (n=42)	34 [32-42]
Sex	
Female	29 (65.9)
Male	15 (34.1)
Type of area in which the practice is located	
Rural	0 (0)
Semirural	9 (20.5)
Urban	35 (79.5)
GP fee regulation	
Yes	44 (100)
No	0 (0)
Secretarial support	38 (86.4)
Secretary at the practice	38 (86.4)
Phone line only	17 (38.6)
Appointments made online	21 (47.7)
Changes in consultation procedures since the COVID-19 epidemic	
Changes	38 (86.4)
No changes	6 (13.6)
Dedicated COVID-19 centre	10 (22.7)
Creation of specific COVID-19 consultations	38 (86.4)
Cancellation of non-COVID-19 consultations	13 (29.6)
Creation of separate COVID-19/non-COVID-19 areas	29 (65.9)
Changes to secretarial support since the COVID-19 epidemic	15 (34.1)
Closure of the secretary's office	6 (13.6)
Phone line only	18 (40.9)
Appointments made online	20 (45.5)
Changes to the waiting room since the COVID-19 epidemic	
No changes	0 (0)
Dedicated areas or arrangements in the waiting room	44 (100)
Closure of the waiting room	0 (0)
Hygiene measures since the COVID-19 epidemic	
More frequent disinfection of reception areas	44 (100)
Alcohol-based hand sanitizer available for patients	44 (100)
Patients provided with face masks if required	39 (88.6)
Protective measures for caregivers since the COVID-19 epidemic	
Gowns	26 (59.1)
Masks	44 (100)
Overshoes	22 (50.0)
Gloves	31 (70.5)
Glasses	31 (70.5)
Hair nets	26 (59.1)

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

GP, general practictioner; MPCC : multiprofessional primary care centre; CHS : community health centre

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	Tables
		(*d*) If applicable, explain how loss to follow-up was addressed	Figure 1
		(*e*) Describe any sensitivity analyses	8
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	25
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study

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Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study.

Running title: Patients with suspected COVID-19 in general practice

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ABSTRACT

Objectives: To describe and compare the initial clinical characteristics of a cohort of patients with suspected COVID-19 managed by general practitioners (GPs); to assess whether 3-month persistent symptoms were more frequent among confirmed cases than among no-COVID cases; and to identify factors predictive of persistent symptoms and adverse outcomes among confirmed cases.

Design and setting: A comparative, prospective, multicentre cohort study in primary care, in the Paris region of France.

Participants: 521 patients aged ≥18 with suspected COVID-19 were enrolled between March and May 2020.

Outcome measures: Initial symptoms, COVID-19 status, persistent symptoms 3 months post-inclusion, and a composite criterion for potentially COVID-19-related events (hospitalization, death, emergency department visits). The final COVID-19 status ("confirmed", "no-COVID", and "uncertain" cases) was determined by the GP after the receipt of the lab test results.

Results: 516 patients were analyzed; 166 (32.2%) were classified into the "confirmed COVID" group, 180 (34.9%) into the "no-COVID" group and 170 (32.9%) in the "uncertain COVID" group. Confirmed cases were more likely to have persistent symptoms than no-COVID cases (*P*=0.09); initial fever/feeling feverish and anosmia were independently associated with persistent symptoms. At 3 months, we observed 16 (9.8%) COVID-19-related hospital admissions, 3 (1.8%) intensive care unit admissions, 13 (37.1%) referrals to an emergency department, and no deaths. Age >70 and/or at least one comorbidity (OR 6.53; 95% CI [1.13-37.84]; *P*=0.036), abnormalities in a lung examination (15.39 [1.61-146.77];

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P=0.057) and two or more systemic symptoms (38.61 [2.30-647.40]; *P*=0.011) were associated with the composite criterion.

Conclusions: Although most COVID-19 patients in primary care had mild disease with a benign course, almost 1 in 6 had persistent symptoms at 3 months. These symptoms were more frequent in the "confirmed COVID" group. Our findings need to be confirmed in a prospective study with longer follow-up.

Keywords: COVID-19, signs and symptoms, cohort studies, risk factors, general practice

Strengths and limitations of this study

- This work is one of the few French studies to have included solely patients managed in primary care early on in the first wave of the COVID-19 pandemic.
- In contrast to most research on COVID-19, our study featured a control group (a "confirmed COVID" group, which was compared with "no-COVID" and "uncertain COVID" groups).
- The large number of primary care centres involved in the study suggests that our results can be extrapolated to the local and regional levels.
- Early on in the pandemic, COVID-19 RT-PCR tests were not widely available; COVID-19 status was not therefore confirmed in all patients.
- The small size of some subgroups (e.g. the subgroup of patients with persistent symptoms) might have led to a lack of statistical power and thus prevented us from drawing formal conclusions in that respect.

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BACKGROUND

The first wave of COVID-19 in France prompted a lockdown from mid-March to mid-May 2020. General practitioners (GPs) were in the front line [1]; they referred severe cases to hospital and managed less severe cases [2]. Early on in the epidemic, researchers sought to describe the COVID-19 patients' demographic and clinical characteristics and their course of disease. However, these studies were fully [3-8] or partly [9] conducted in hospital. The most frequently reported initial signs were fever, cough, and dyspnoea [3]. Anosmia and ageusia were also prevalent, and their concomitant presence was quite specific for a SARS-CoV-2 infection [10-12]. At the time when our study data were collected, some researchers had highlighted "long COVID-19" as an entity with some or all the following symptoms 3 to 12 months after disease onset [8,13,14]: persistent asthenia, headache, dyspnoea, sleep difficulties, anxiety or depression, and anosmia [13,14]. The significance of these symptoms is subject to debate, particularly since the literature data were somewhat contradictory; however, some researchers have suggested that these symptoms are correlated with the severity of the initial disease [8] and the number of initial symptoms [15]. Most of these studies of "long COVID-19" estimated the frequency of persistent symptoms or adverse outcomes in hospital cohorts of patients with a confirmed diagnosis of COVID-19 but lacked a control group [3,4,7-8]. Hence, these studies were not representative of patients in primary care – even though most COVID-19 cases are diagnosed by GPs [2]. Therefore, the objectives of the present study were to (i) describe and compare the initial clinical characteristics of a cohort of patients with suspected COVID-19 managed by GPs and whose COVID-19 status ("confirmed", "no-COVID", and "uncertain" cases) was determined by the GP after he/she had received the lab test results; (ii) determine whether persistent symptoms at 3 months were more frequent among confirmed cases than among no-COVID cases; and (iii) identify factors predictive of persistent symptoms and adverse outcomes among confirmed cases.

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METHODS

Patient and public involvement

All patients received an information sheet and gave their verbal consent to participation. They were not involved in the study design, conduct or reporting or the plans for dissemination.

Study design

This multicentre, prospective cohort study was conducted in four counties in the Paris region: Val-de-Marne, Seine-et-Marne, Essonne, and Seine-Saint-Denis. Forty-four GPs were recruited from multiprofessional primary care practices affiliated with the Faculty of Health at Université Paris-Est Créteil (Créteil, France), because some of the GPs tutored the university's medical students. The GPs' characteristics are summarized in the Online Supplement 1 Table S1.

Population

During the first wave's lockdown period, we prospectively included all consecutive adult patients who consulted one of the participating GPs for a suspected COVID-19 infection. The exclusion criteria were age under 18, no suspicion of COVID-19, and residence in an institution. The first patient was included on March 6th, 2020, and the last was included on May 12th, 2020. Patients were followed up for three months, and study data were extracted on October 22nd, 2020.

Data sources

The patients' data were extracted from the GPs' electronic medical records. The clinical criteria for a diagnosis of COVID-19 were left to the GP's discretion. Patients were followed

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up as usual by their GP, and all consultations with healthcare professionals and/or hospital visits were registered. Three months after inclusion, the GP phoned or visited patients to collect data on persistent symptoms or recovery. For confirmed cases, they also looked for COVID-19-related hospital admissions, referrals to an emergency department, admissions to an intensive care unit, and deaths. These data were completed with information from hospital discharge reports, if available.

COVID-19 status

The GPs prescribed SARS-CoV-2 serology and/or RT-PCR tests and/or a CT scan of the chest, in line with the French national guidelines [16-20]. During the first wave of COVID-19 (mid-March to mid-May 2020), RT-PCR and serology tests were not widely available. An RT-PCR test was recommended for patients with severity criteria and/or with comorbidities, and for healthcare professionals [16-17]. The French national guidelines recommended a CT scan if the patient had trouble breathing, in order to assess the extent of any lung damage and to have a reference examination [20]. Serology tests became available from May 2020 and were prescribed *a posteriori* to (i) patients with compatible symptoms and who had not had an RT-PCR test and (ii) patients with a negative RT-PCR test [17-18].

The patient's COVID-19 status was ultimately classified by the GP as "confirmed COVID", "no-COVID", or "uncertain COVID" after he/she had received the lab test results. Confirmed COVID status was defined as a positive RT-PCR and/or serology test, and/or a chest CT result suggestive of COVID-19. "No-COVID" status was defined as both a negative RT-PCR test and a negative serology test, a negative RT-PCR test in the absence of a positive serology test or a positive chest CT, or a negative serology test in the absence of a positive RT-PCR test or a positive chest CT. "Uncertain COVID" status was defined as the presence of suggestive symptoms and the absence of both RT-PCR and serology test and chest CT results.

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Outcomes

We considered the two following outcomes: the persistence of symptoms three months after study inclusion (as assessed by the GP), and (for confirmed cases only) adverse outcomes defined by a composite criterion that included COVID-19-related hospital admissions, referral to an emergency department, intensive care unit admissions, and deaths. The relationship with COVID-19 was determined from hospital records. The GP identified and recorded the patient's persistent symptoms (if any), according to his/her usual clinical practice. We asked the GPs three questions: *"Do you consider that the patient has been cured?"*, *"If not, which symptoms persisted?"*, and *"Do you attribute those symptoms to the initial disease?"*. Persistent symptoms (if any) were not rated on a scale or using a questionnaire.

Potential factors predictive of 3-month persistent symptoms and adverse outcomes

Among confirmed cases, the following variables (Appendix 1) collected at the initial consultation were considered as potentially predictive factors for persistent symptoms and adverse outcomes: demographic characteristics (age, sex, being a caregiver), smoking, obesity, comorbidities, initial COVID-19 symptoms, the number of symptoms, systemic symptoms (i.e., fever, headache, asthenia, and skin symptoms), ENT symptoms, and data from an initial clinical examination.

Statistical analysis

Qualitative variables were described as the number (percentage), and quantitative variables were described as the median [interquartile range (IQR)] or tertile values, as appropriate. Univariate analyses used the chi-2 test, the Fisher's test or the Kruskal-Wallis test, as appropriate. Given the hierarchical nature of the data (level 1: the patient; level 2: the GP),

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we used multilevel logistic models [21] to estimate univariate and multivariate odds ratios (ORs) and their 95% confidence intervals (CIs).

The distribution of the patient initial characteristics was compared across the three groups (confirmed, no-COVID, and uncertain). When the *P*-value was ≤0.15, we used age-adjusted multilevel logistic models to perform post-hoc pairwise comparisons for confirmed cases vs. no-COVID cases on one hand, and between confirmed cases and uncertain cases on the other. Next, we compared the prevalence of persistent symptoms in the confirmed vs. no-COVID groups. To assess predictive factors for 3-month persistent symptoms and adverse outcomes among the COVID confirmed cases, we compared the groups with vs. without persistent symptoms and with vs. without adverse outcomes, in univariate analyses. Factors with *P*<0.15 in the univariable analysis were considered for inclusion in multivariable multilevel logistic analyses after the assessment of confounders and interactions in bivariate models. As "older age" and "at least one comorbidity" were highly correlated, we built the following composite variable: "age>70 and/or at least one comorbidity". Lastly, in a sensitivity analysis, patients with both anosmia and ageusia but no test results were moved from the "uncertain COVID" group to the "confirmed COVID" group, and similar analyses were performed. All tests were two-sided, and the threshold for statistical significance was set to *P*≤0.05. We used the false discovery rate method for post-hoc analyses. All analyses were performed with Stata software (version 14.2, StataCorp LLC, College Station, TX, USA).

Ethics

The study database was registered with the French National Data Protection Commission (reference: 2211627 v0). The study protocol was approved by an independent ethics committee (*Comité de Protection des Personnes Est IV* (Strasbourg, France); reference: IDRCB 2020-A01693-36).

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RESULTS

Study population

During the study period, 521 patients were included. Of these, 516 were analysed: 166 (32.2%) were classified as "confirmed COVID", 180 (34.9%) were classified as "no-COVID", and 170 (32.9%) were classified as "uncertain COVID" (Figure 1). The characteristics of the groups' test results and disease classifications are summarized in Supplementary 2 Table S2.

Characteristics of the population, and intergroup comparisons

In the overall population, median [IQR] age was 43 y [33-56], 62.2% were female, 12.5% were caregivers, and 40.7% had at least one comorbidity (Appendix 1). The three groups differed significantly with regard to the following initial characteristics: age, being a caregiver, having been in contact with a positive case, having at least one comorbidity, fever or feeling feverish, having muscle ache, chest pain, dyspnoea, a sore throat, anosmia, agueusia, diarrhoea, and the number of systemic symptoms.

Relative to the no-COVID group, confirmed cases were significantly older and were more likely to be caregivers, to have been in contact with a confirmed case of COVID-19, and to have had anosmia or agueusia. A non-significant trend towards an association with a higher number of systemic symptoms was also observed. In contrast, chest pain and sore throat were less frequent in the "confirmed case" group.

Relative to the uncertain COVID group, confirmed cases were significantly older and were more likely to be caregiver, to have been in contact with a confirmed case of COVID-19, to have had fever or feeling feverish, muscle ache, anosmia, agueusia, diarrhoea and more than two systemic symptoms. In contrast, they were less likely to be male.

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Three-month persistent symptoms in the "confirmed COVID" and "no-COVID" groups

Overall, the percentage of three-month persistent symptoms was higher in the confirmed COVID group than in the no-COVID group, although the difference was not statistically significant (*P*=0.090) (Table 1). The confirmed COVID group was more likely to have persistent anosmia (OR=8.51; 95% CI [1.03-70.43]; *P*=0,047). Similar results were found in the sensitivity analysis (Table 1).

Predictive factors for 3-month persistent symptoms and adverse outcomes in confirmed COVID cases

In a univariate analysis, the factors associated with 3-month persistent symptoms were fever or feeling feverish and anosmia (Table 2). In a multivariate analysis, fever and anosmia were independently associated with 3-month persistent symptoms. Similar results were found in the sensitivity analysis (OR_{fever}=8.49; 95% CI [1.34-53.83]; *P*=0,023 and $OR_{anosmia}$=4.24; 95% CI [0.99-18.23]; *P*=0,052).

Among the confirmed cases, we observed 16 (9.8%) COVID-19-related hospital admissions, 3 (1.8%) admissions to an intensive care unit, 13 (37.1%) referrals to an emergency department, and no deaths. In a univariate analysis, patients with 3-month adverse outcomes were older, and more likely to have at least one comorbidity (hypertension, dyslipidaemia, diabetes, and cardiovascular disease), fever or feeling feverish, and a higher number of systemic symptoms (Table 3). A trend was observed for abnormalities in a lung clinical examination. In a multivariate analysis, the composite variable "age >70 and/or at least one comorbidity", abnormalities in a lung clinical examination and two or more systemic symptoms were independently associated with 3-month adverse outcomes (Table 3). Similar results were found in the sensitivity analysis (OR_{fever}=6.72; 95% CI [1.24-36.54]; *P*=0,027;

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$OR_{\geq 2 \text{ systemic symptoms}}$=44.52; 95% CI [2.67-741.89]; *P*=0,008; and $OR_{\text{abnormalities in a lung examination}}$=17.58; 95% CI [1.80-171.63]; *P*=0.047).

DISCUSSION

Principal findings

We included 516 patients managed by GPs for suspected COVID-19 during the first wave of the disease in France: 32.2% were classified as "confirmed COVID" cases, 34.9% were classified as "no-COVID" cases, and 32.9% were classified as "uncertain COVID" cases. The clinical course was mainly benign, although the hospital admission rate (with no deaths) was 9.8% in the "confirmed COVID" group. In the latter group, the variable "age >70 and/or at least one comorbidity", abnormalities in a lung examination, and two or more systemic symptoms were independently associated with 3-month hospital admission and referral to an emergency department. Moreover, "confirmed COVID" patients tended to have more persistent symptoms at 3 months - mainly anosmia and "other persistent symptoms". Fever or feeling feverish, and anosmia were independently associated with the persistence of symptoms.

Strengths and weaknesses of the study

This is one of the few studies to have included solely patients consulting in general practice; most longitudinal studies of COVID-19 patients assessed hospital-based or mixed cohorts. Moreover, our assessment of a prospective multicentre cohort recruited at different primary care health centres means that our results can be more readily extrapolated to the local or regional level. Another study strength was our comparison of "confirmed COVID", "no-COVID" and "uncertain COVID" groups; this provided a more accurate comparison of the

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initial and subsequent signs and symptoms of COVID-19. The "no COVID" group was particularly relevant for comparing the prevalence of persistent symptoms because it probably comprised patients with other viral diseases.

However, our study had some limitations. Selection bias might have been present because the RT-PCR test was only initially recommended for patients with severity criteria and/or with comorbidities, and for healthcare professionals. This may explain some of the demographic characteristics of confirmed cases. However, this bias was limited by the prescription of serology tests *a posteriori* to patients with compatible symptoms and who had not had an RT-PCR test and to patients with a negative RT-PCR test. We did not include under-18 patients and institutionalized patients. The study was limited to the greater Paris region and so might not be representative of the French population as a whole. Moreover, the groups' size might have led to a lack of statistical power. Given the small number of patients with persistent symptoms, the corresponding results should be interpreted with caution (especially the ORs with very broad CIs). The methods for determining the presence or absence of persistent symptoms were left to the GP's discretion; the use of particular questionnaires or scales was not imposed on them. This lack of standardization might have influenced the estimated prevalence of persistent symptoms. However, this unconstrained type of assessment was similar to that used in the GPs' routine clinical medical practice. Lastly, COVID-19-related hospital admissions were recorded; it would have been useful to collect data on the symptom burden associated with all-cause hospital admissions.

Comparison with other studies

The demographic characteristics of our COVID-19 patients consulting in general practice were similar to those in the literature, particularly with regard to the mean age (43 in our

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study and in Yordanov et al.'s study [22]), the proportion of caregivers [23-24], and the most prevalent comorbidities (hypertension, and diabetes) [20]. Several studies of ambulatory patients have shown that systemic symptoms (including asthenia, fever, cough, myalgia, and headaches) were frequent [4,25-27]. Anosmia and ageusia were also frequent and appeared later in the course of disease. Some experts consider that the anosmia-ageusia combination is specific for COVID-19 [12]. Digestive tract symptoms were less frequent [4,6,28-30]. Our patients also varied with regard to the signs in the GPs' clinical examination (including abnormalities in a lung examination), as found in systematic reviews [12,31]. In line with our results, most studies of outpatients have found that the course of the disease is benign and that hospital admission is not required [17,22,23]. As found in the present research, literature data have shown that a higher frequency of negative outcomes (hospital admission and death) is associated with older age [32-33] and with comorbidities like cardiovascular disease and diabetes [22,33-34]. In contrast to another study, we did not find an association with male sex [35]. However, no other studies have found that more than two systemic symptoms at the initial GP visit and abnormalities in a lung examination are predictive of an adverse outcome. These present findings and the literature data [12,31] highlight the need for a clinical consultation with the GP.

It has been widely reported that patients can experience persistent symptoms more than four weeks after an episode of COVID-19 [36]. Here, we observed a non-significant trend toward a greater prevalence of persistent symptoms at 3 months in the "confirmed COVID" group (15.7%), vs. the no-COVID group (9.6%). This finding is in line with the results of a UK study in which 13.7% of outpatients had symptoms that persisted for at least 12 weeks [36]. However, the association remained significant in our "confirmed COVID" group for anosmia and "other symptoms" (i.e. deep vein thrombosis, alopecia, palpitations, feeling feverish, and memory impairments), as also reported elsewhere [37]. A recent, large cohort study

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suggested that self-reported infection was positively associated with persistent physical symptoms, whereas a positive serology test result for SARS-COV-2 was positively associated only with persistent anosmia [13]. Furthermore, it appears that one of the factors determining the presence of persistent symptoms in our COVID patients was the presence of fever during the initial GP visit. This association with fever has only previously been found in one study of elderly people [38] but not in other studies [39].

In our study, a comparison at 3 months showed that some persistent symptoms (asthenia, cough, chest pain, and dyspnoea) were not significantly more frequent in the "confirmed COVID" group - suggesting they were not specific for "long COVID-19". Asthenia and dyspnoea were the two most common persistent symptoms in hospitalized and non-hospitalized patients [40]. However, we observed asthenia and dyspnoea respectively in around only 4% and 3% of our "confirmed COVID" patients, and with much the same frequency as in no COVID patients (4.5% and 4.5%, respectively). Outpatient studies with a control group found the presence of persistent symptoms up to 10 [41] and 12 months [42] after mild COVID-19, with miscellaneous symptoms: asthenia, headaches, smell and taste disorders, dyspnoea, memory disorders, insomnia, and difficulty concentrating [41-42]. The French health authorities also included neurological, cardiothoracic and sensory disorders in the list of persistent symptoms [43].

The results of these "long COVID-19" studies are relatively disparate and appear to show that this entity is non-specific because of the multisymptomatic, fluctuating nature of the clinical manifestations [43].

Implications for clinicians and policymakers

It is important to provide GPs with primary-care-specific data that enable them to optimize patient management. GPs have an essential role in combating the pandemic [44] and diagnose

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most patients with COVID-19 [2]. Identifying prognostic factors and examining patients for clinical abnormalities could help to detect patients at risk, set up follow-up procedures, and anticipate possible worsening [2,45]. These strategies might be needed in France, with a view to enabling primary care to withstand future health emergencies and pandemics, as has been mentioned in Australia, New Zealand, Canada, the Netherlands, the UK, and the US [46]. The trend towards more frequent persistent symptoms in patients with COVID-19 (more specifically, anosmia and "other symptoms") suggests that follow-up by the GP should take account of the disease's impact on quality of life, overall health and life context via a patient-centred approach [47].

Unanswered questions and future research

Our findings (notably concerning persistent symptoms) need to be confirmed in the longer term and in other patient populations (e.g. institutionalized people, children, and adolescents). Our study was partly based on electronic medical records and showed that primary care can provide important public health data. This work could be expanded with patient surveys and GP interviews, so as to combine real-time data on patients' symptoms and adverse outcomes with patient responses to public health messaging and information on the GPs' adaptive coping mechanisms [46].

CONCLUSIONS

Cases of COVID-19 seen in primary care have an essentially benign course. However, age >70 and/or at least one comorbidity, abnormalities in a lung examination, and a higher number of systemic symptoms were associated with hospital admission and referral to an

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emergency department. Our results reinforce the need for a face-to-face medical consultation by the GP to identify patients at risk of severe disease. Almost 1 in 6 COVID patients had persistent symptoms at 3 months - emphasizing the need for an overall, patient-centred approach. This frequency of persistent symptoms tended to be higher in COVID patients than in no-COVID cases. Anosmia and a group of rarer symptoms were more prevalent in the "confirmed COVID" group. Asthenia, chest pain, cough, and dyspnoea were also present in the other groups and might not be specific for a possible "long COVID-19". Our findings in primary care need to be confirmed in prospective studies with a longer follow-up period.

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Supplementary and raw data: The characteristics of the participating GPs and their practices are presented in Online supplement 1. Table S1. The characteristics of the study population and the univariate comparison of the three patient groups are presented in Appendix 1. The characteristics of the test results for the three groups of patients are presented in Online supplement 2. Table S2.

REFERENCES

[1] Saint-Lary O, Gautier S, Le Breton J, Gilberg S, Frappé P, et al. How GPs adapted their practices and organisations at the beginning of COVID-19 outbreak: a French national observational survey. BMJ Open. 2020;10:e042119. doi: 10.1136/bmjopen-2020-042119

For peer review only

[2] Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. BMJ. 2020 Mar 25;368:m1182. doi: 10.1136/bmj.m1182.

[3] Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ. 2020 May 29;369:m1996. doi: 10.1136/bmj.m1996.

[4] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020 May 22;369:m1985. doi: 10.1136/bmj.m1985.

[5] Tostmann A, Bradley J, Bousema T, Yiek WK, Holwerda M, Bleeker-Rovers C, et al. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, March 2020. Euro Surveill. 2020 Apr;25(16):2000508. doi: 10.2807/1560-7917.ES.2020.25.16.2000508.

[6] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020 Jul;75(7):1730-1741. doi: 10.1111/all.14238. Epub 2020 Feb 27.

[7] Lechien JR, Chiesa-Estomba C, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020 Aug;277(8):2251-2261. doi: 10.1007/s00405-020-05965-1. Epub 2020 Apr 6.

[8] Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 6;397(10270):220-232. doi: 10.1016/S0140-6736(20)32656-8. Epub 2021 Jan 8.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

[9] Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020 Sep;288(3):335-344. doi: 10.1111/joim.13089. Epub 2020 Jun 17.

[10] Villerabel C, Makinson A, Jaussent A, Picot M, Nègre-Pagès L, Morquin D, et al. Dépistage de la COVID-19 : valeurs diagnostiques d'une anosmie rapportée ou objectivée par un test clinique. Med Mal Infect. 2020 Sep; 50(6): S78.

[11] Zayet S, Klopfenstein T, Royer P, Toko L, Kadiane-Oussou N, Gendrin V. Sensibilité, spécificité et valeurs prédictives des signes fonctionnels de l'infection par SARS-CoV-2. Med Maladies Infect. 2020 Sep;50(6) :S77.

[12] Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MMG, et al. Cochrane COVID-19 Diagnostic Test Accuracy Group. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD013665. DOI: 10.1002/14651858.CD013665.pub2.

[13] Matta J, Wiernik E, Robineau O, Carrat F, Touvier M, Severi G, et al. Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic. JAMA Intern. Med. JAMA Intern Med . 2021 Nov 8;e216454. doi: 10.1001/jamainternmed.2021.6454.

[14] Nehme M, Braillard O, Chappuis F, Courvoisier DS, Guessous I; CoviCare Study Team. Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in an Outpatient Setting. Ann Intern Med. 2021 Sep;174(9):1252-1260. doi:10.7326/M21-0878. Epub 2021 Jul 6.

For peer review only

[15] Cirulli ET, Schiabor Barrett KM, Riffle S, Bolze A, Neveux I, Dabe S, et al. (2020) Long-term COVID-19 symptoms in a large unselected population. medRxiv: 2020100720208702.

[16] French High Council of Public Health. Haut Conseil de la Santé Publique, 2020. Available: https://solidarites-sante.gouv.fr/IMG/pdf/hcsp_sars-cov2-priorisationtestsdiagnostiques-2020-03-11-2.pdf

[17] French High Autority for Health. Réponses rapides dans le cadre de la COVID-19. Prise en charge de premier recours des patients atteints de Covid-19. Haute Autorité de Santé, 2020 Available: https://www.has-sante.fr/upload/docs/application/pdf/2022-02/reco453_rr_covid_19_premier_recours_20220216_mel.pdf

[18] French High Autority for Health. Premières indications pour les tests sérologiques du COVID-19. Haute Autorité de Santé, 2020. Available: https://www.has-sante.fr/jcms/p_3182370/fr/premieres-indications-pour-les-tests-serologiques-du-covid-19

[19] French Society of Radiology. Epidémie de COVID-19 : POINT SUR L'IMAGERIE. Société Française de Radiologie, 2020. Available: https://ebulletin.radiologie.fr/actualites-covid-19/epidemie-covid-19-point-limagerie

[20] French High Autority for Health. Réponses rapides dans le cadre de la COVID-19 - Place du scanner thoracique. Haute Autorité de Santé, 2020. Available: https://www.has-sante.fr/upload/docs/application/pdf/2020-04/reponse_rapide_codid-19_indication_tdm_mel2.pdf

[21] Hox JJ, Moerbeek M, van de Schoot R. Multilevel Analysis, techniques and applications. Third Edition, 2018. Routledge, New York.

For peer review only

[22] Yordanov Y, Dinh A, Bleibtreu A, Mensch A, Lescure FX, Debuc E, et al.. Clinical characteristics and factors associated with hospital admission or death in 43 103 adult outpatients with coronavirus disease 2019 managed with the Covidom telesurveillance solution: a prospective cohort study. Clin Microbiol Infect. 2021 Aug;27(8):1158-1166. doi: 10.1016/j.cmi.2021.04.010. Epub 2021 Apr 27.

[23] Wu Z, McGoogan MJ. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-1242. doi: 10.1001/jama.2020.2648.

[24] Riccardo F, Ajelli M, Andrianou XD, Bella A, Del Manso M, Fabiani M, et al. Epidemiological characteristics of COVID-19 cases and estimates of the reproductive numbers 1 month into the epidemic, Italy, 28 January to 31 March 2020. Euro Surveill. 2020 Dec;25(49):2000790. doi: 10.2807/1560-7917.ES.2020.25.49.2000790.

[25] Lapostolle F, Schneider E, Vianu I, Dollet G, Roche B, Berdah J, et al. Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study. Intern Emerg Med. 2020 Aug;15(5):813-817. doi: 10.1007/s11739-020-02379-z. Epub 2020 May 30.

[26] Khan M, Khan H, Khan S, Nawaz M. Epidemiological and clinical characteristics of coronavirus disease (COVID-19) cases at a screening clinic during the early outbreak period: a single-centre study. J Med Microbiol. 2020 Aug;69(8):1114-1123. doi:10.1099/jmm.0.001231.

[27] Ayaz CM, Dizman GT, Metan G, Alp A, Unal S. Out-patient management of patients with COVID-19 on home isolation. Infez Med. 2020 Sep 1;28(3):351-356.

[28] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24.

[29] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20. DOI: 10.1056/NEJMoa2002032

[30] Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer S, et al. High Prevalence of Concurrent Gastrointestinal Manifestations in Patients With Severe Acute Respiratory Syndrome Coronavirus 2: Early Experience from California. Gastroenterology. 2020 Aug;159(2):775-777. doi: 10.1053/j.gastro.2020.04.008. Epub 2020 Apr 10.

[31] Izcovich A, Ragusa MA, Tortosa F, Marzio MAL, Agnoletti C, Bengolea A, et al. Correction: Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLOS ONE 2022;17(5): e0269291. https://doi.org/10.1371/journal.pone.0269291

[32] Dres M, Hajage D, Lebbah S, Kimmoun A, Pham T, Béduneau G, et al. Characteristics, management, and prognosis of elderly patients with COVID-19 admitted in the ICU during the first wave: insights from the COVID-ICU study : Prognosis of COVID-19 elderly critically ill patients in the ICU. Ann Intensive Care. 2021 May 14;11(1):77. doi: 10.1186/s13613-021-00861-1.

[33] Tenreiro P, Ramalho A, Santos P. COVID-19 patients followed in Portuguese Primary Care: a retrospective cohort study based on the national case series. Fam Pract. 2022 Jan 19;39(1):52-58. doi: 10.1093/fampra/cmab098.

[34] Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira R, Weill A, et al. Maladies chroniques, états de santé et risque d'hospitalisation et de décès hospitalier pour COVID-19: analyse comparative de données des deux vagues épidémiques de 2020 en France à partir d'une cohorte de 67 millions de personnes. 2021. Available: https://www.epi-

phare.fr/app/uploads/2021/07/epi-phare_risques_hospitalisations_deces_covid19_20210721.pdf

[35] Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020 Dec 9;11(1):6317. doi: 10.1038/s41467-020-19741-6.

[36] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615. doi: 10.1038/s41591-021-01283-z. Epub 2021 Mar 22.

[37] French High Council of Public Health. Avis relatif aux symptômes cliniques persistants au décours d'un COVID-19. Haut Conseil de la Santé Publique, 2021. Available: https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1037

[38] Sudre CH, Murray B, Varsaysky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long-COVID. Nat Med. 2021 Jun;27(6):1116. doi: 10.1038/s41591-021-01361-2.

[39] Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. Lancet Reg Health Eur. 2021 Jul;6:100122. doi: 10.1016/j.lanepe.2021.100122. Epub 2021 May 18.

[40] Rajan S, Khunti K, Alwan N, Steves C, Greenhalgh T, MacDermott N, et al. In the wake of the pandemic: Preparing for Long COVID. 2021. Available: https://apps.who.int/iris/bitstream/handle/10665/339629/Policy-brief-39-1997-8073-eng.pdf

For peer review.

[41] Desgranges F, Tadini E, Munting A, Regina J, Filippidis P, Viala B, et al. Post-COVID-19 Syndrome in Outpatients: a Cohort Study. J Gen Intern Med. 2022 Jun;37(8):1943-1952. doi: 10.1007/s11606-021-07242-1. Epub 2022 Mar 22. PMID: 35319081; PMCID: PMC8939498.

[42] Nehme M, Braillard O, Chappuis F, Courvoisier DS, Kaiser L, Soccal PM, et al. One-year persistent symptoms and functional impairment in SARS-CoV-2 positive and negative individuals. J Intern Med. 2022 Jul;292(1):103-115. doi: 10.1111/joim.13482. Epub 2022 Mar 31. PMID: 35555926; PMCID: PMC9115262.

[43] French High Autority for Health. Symptômes prolongés suite à une Covid-19 de l'adulte - Diagnostic et prise en charge. Haute Autorité de Santé, 2021. Available: https://www.has-sante.fr/jcms/p_3237041/fr/symptomes-prolonges-suite-a-une-covid-19-de-l-adulte-diagnostic-et-prise-en-charge

[44] Sarti TD, Lazarini WS, Fontenelle LF, et al. What is the role of primary health care in the COVID-19 pandemic? Epidemiol Serv Saude 2020;29:e2020166.

[45] Prado NMBL, Biscarde DGDS, Pinto Junior EP, Santos HLPCD, Mota SEC, Menezes ELC, et al. Primary care-based health surveillance actions in response to the COVID-19 pandemic: contributions to the debate Cien Saude Colet. 2021 Jul;26(7):2843-2857. doi: 10.1590/1413-81232021267.00582021. Epub 2021 Mar 29.

[46] Huston P, Campbell J, Russell G, Goodyear-Smith F, Phillips RL Jr, van Weel C, Hogg W. COVID-19 and primary care in six countries. BJGP Open. 2020 Oct 27;4(4):bjgpopen20X101128. doi: 10.3399/bjgpopen20X101128. Print 2020 Oct.

[47] Stewart M. Patient-Centred Medicine: Transforming the Clinical Method. 3rd ed.

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London, CRC Press 2019; 442p.

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Figure 1. Study flow diagram

Figure legend: GP: general practitioner

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Table 1. Comparison of 3-month persistent symptoms between Covid vs no Covid groups (N=346)

		Main analysis				Sensitivity analysis	
	No COVID n=180	**Confirmed COVID n=166**	**p[a]**	**OR [95% CI]**	**p[b]**	**OR [95% CI] (N=195 vs 180)**	**p[b]**
Any persistent symptom combined (n=177/159//182)	17 (9.6)	25 (15.7)	0.090	1.66 [0.86-3.23]	0.133	1.67 [0.88-3.19]	0.118
Asthenia (n=177/159//182)	8 (4.5)	6 (3.8)	0.733				
Cough (n=177/159//182)	3 (1.7)	4 (2.5)	0.712				
Dyspnoea (n=177/159//182)	8 (4.5)	5 (3.1)	0.514				
Chest pain (n=177/159//182)	3 (1.7)	3 (1.9)	1				
Anosmia (n=177/159//182)	1 (0.6)	7 (4.4)	0.029	8.51 [1.03-70.43]	0.047	8.36 [1.03-67.68]	0.047
Agueusia (n=177/159//182)	3 (1.7)	4 (2.5)	0.712				
Other symptoms (n=177/159//182)	1 (0.6)	7 (4.4)	0.029	7.02 [0.84-58.29]	0.071	7.62 [0.94-61.87]	0.058
Deep vein thrombosis	0 (0)	1 (14.3)					
Alopecia	0 (0)	1 (14.3)					
Myalgia	0 (0)	1 (14.3)					
Palpitations	0 (0)	1 (14.3)					
Pruritus, rash	1 (100)	0 (0)					
Feeling feverish	0 (0)	2 (28.6)					
Memory impairments	0 (0)	1 (14.3)					

Data are quoted as the n (%)

a The p-values were obtained from a chi-squared test or Fisher's exact test

b Age adjusted multilevel logistic regression

OR: odds ratio; CI: confidence interval

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Table 2. Multilevel uni- and multivariate analysis of factors associated with 3-month persistent symptoms among patients with confirmed COVID-19 (n=159)

	3-month persistent symptoms			Univariate analysis		Multivariate analysis (final model)	
	No, n=134 (84.3%)	Yes, n=25 (15.7%)	p[a]	OR [95% CI]	p[b]	OR [95% CI]	p[b]
Age (years)	48 [39-58]	51 [41-59]	0.509				
Male sex	49 (36.6)	6 (24.0)	0.225				
Caregivers (n=120/22)	24 (20.0)	5 (22.7)	0.776				
Smoking (n=38/10)	14 (36.8)	2 (20.0)	0.460				
At least one comorbidity (n=133/25)	60 (45.1)	13 (52.0)	0.526				
Dyslipidaemia (n=133/25)	5 (3.8)	2 (8.0)	0.306				
Obesity (n=47/9)	18 (38.3)	5 (55.6)	0.464				
Hypertension (n=133/25)	23 (17.3)	3 (12.0)	0.769				
Diabetes (n=133/25)	6 (4.5)	1 (4.0)	1				
Cardiovascular disease (n=133/25)	11 (8.3)	3 (12.0)	0.466				
Asthma (n=133/25)	11 (8.3)	4 (16.0)	0.261				
Age > 70 and/or presence of at least one comorbidity (n=133/25)	61 (45.9)	13 (52.0)	0.573				
Symptoms at the initial consultation							
Fever or feeling feverish (n=122/22)	59 (48.4)	17 (77.3)	0.012	3.63 [1.26-10.46]	0.017	6.93 [1.62-29.53]	0.009
Asthenia (n=51/7)	42 (82.4)	7 (100)	0.581				
Muscle ache (n=99/19)	68 (68.7)	16 (84.2)	0.171				
Headache (n=88/16)	49 (55.7)	10 (62.5)	0.613				
Rhinorrhoea (n=86/17)	42 (48.8)	11 (64.7)	0.232				
Cough (n=121/23)	93 (76.9)	21 (91.3)	0.163				
Expectorations (n=62/15)	15 (24.2)	3 (20.0)	1				
Chest pain (n=80/17)	15 (18.8)	4 (23.5)	0.737				
Dyspnoea at rest and/or on exertion (n=96/16)	29 (30.2)	5 (31.3)	1				
Sore throat (n=82/16)	36 (43.9)	6 (37.5)	0.636				
Anosmia (n=81/15)	32 (39.5)	10 (66.7)	0.051	3.06 [0.96-9.797]	0.059	4.79 [1.30-17.66]	0.019
Agueusia (n=73/17)	30 (41.1)	11 (64.7)	0.078	2.63 [0.88-7.88]	0.085		
Nausea and/or vomiting (n=77/17)	12 (15.6)	1 (5.9)	0.451				
Diarrhoea (n=86/18)	25 (29.1)	5 (27.8)	0.912				
Abdominal pain (n=31/8)	6 (19.4)	0 (0)	0.313				
Number of symptoms (tertile; n=132/25)			0.108		0.130		
≤4	72 (54.5)	8 (32.0)		1 (ref)			
5	21 (15.9)	6 (24.0)		2.57 [0.80-8.24]			
>5	39 (29.6)	11 (44.0)		2.54 [0.94-6.84]			
Number of systemic symptoms (tertile; n=132/25)			0.355				
≤1	45 (34.1)	7 (28.0)					

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2-3	70 (53.0)	12 (48.0)	
>3	17 (12.9)	6 (24.0)	
Number of ENT symptoms (tertile; n=132/25)			0.189
0	47 (35.6)	6 (24.0)	
1	46 (34.8)	7 (28.0)	
>1	39 (29.6)	12 (48.0)	
Clinical examination			
Temperature>38°C			0.375
No	77 (57.5)	11 (44.0)	
Yes	14 (10.4)	4 (16.0)	
Not reported or missing	43 (32.1)	10 (40.0)	
Respiratory rate (per minute) (n=27/8)	20 [18-20]	19 [15-20]	0.434
SaO2 (%) (n=80/12)	98 [97-99]	98 [97-98.5]	0.624
Abnormalities in a lung examination			0.261
No	74 (55.2)	10 (40.0)	
Yes	14 (10.5)	2 (8.0)	
Not reported or missing	46 (34.3)	13 (52.0)	

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

a The p-values were obtained from a chi-squared test or the Fisher's exact test for qualitative variables, and from the Mann-Whitney test for quantitative variables

b Multilevel logistic regression; the multivariate model included the following variables: fever or feeling feverish and anosmia

ENT: ear nose throat; SaO_2: arterial oxygen saturation; OR: odds ratio; CI: confidence interval

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Table 3. Multilevel uni- and multivariate analysis of factors associated with 3-month composite criterion among patients with confirmed COVID-19 (n=165)

				Univariate analysis		Multivariate analysis (final model)	
	No composite criterion n=147 (89.1%)	Composite criterion n=18 (10.9%)	p[a]	OR [95% CI]	p[b]	OR [95% CI]	p[b]
Age (years)	47 [37-58]	62.5 [50-78]	<0.001	1.08 [1.03-1.13]	0.003		
Male sex	49 (33.3)	9 (50.0)	0.162				
Caregivers (n=133/15)	29 (21.8)	1 (6.7)	0.307				
Smoking (n=46/6)	14 (30.4)	2 (33.3)	1				
At least one comorbidity (n=145/18)	63 (43.5)	13 (72.2)	0.021	4.04 [1.16-14.00]	0.028		
Dyslipidaemia (n=145/18)	4 (2.8)	3 (16.7)	0.030	8.82 [1.28-60.64]	0.027		
Obesity (n=53/5)	22 (41.5)	1 (20.0)	0.639				
Hypertension (n=145/18)	21 (14.5)	7 (38.9)	0.017	3.71 [1.19-11.53]	0.023		
Diabetes (n=145/18)	4 (2.8)	3 (16.7)	0.030	8.23 [1.32-51.34]	0.024		
Cardiovascular disease (n=145/18)	10 (6.9)	6 (33.3)	0.003	7.51 [1.95-28.93]	0.003		
Asthma (n=145/18)	13 (9.0)	2 (11.1)	0.673				
Age > 70 and/or presence of at least one comorbidity (n=145/18)	64 (44.1)	13 (72.2)	0.024	3.92 [1.13-13.60]	0.032	6.53 [1.13-37.84]	0.036
Symptoms at the initial consultation							
Fever or feeling feverish (n=133/17)	66 (49.6)	14 (82.4)	0.011	4.68 [1.24-17.79]	0.023		
Asthenia (n=48/12)	37 (77.1)	12 (100)	0.099	-	-	-	-
Muscle ache (n=111/11)	75 (67.6)	10 (90.9)	0.170				
Headache (n=99/8)	55 (55.6)	4 (50.0)	1				
Rhinorrhoea (n=99/9)	51 (51.5)	4 (44.4)	0.740				
Cough (n=133/15)	108 (81.2)	10 (66.7)	0.188				
Expectorations (n=74/6)	15 (20.3)	3 (50.0)	0.124	4.73 [0.48-47.01]	0.184		
Chest pain (n=92/10)	18 (19.6)	1 (10.0)	0.683				
Dyspnoea at rest and/or on exertion (n=103/13)	30 (29.1)	5 (38.5)	0.528				
Sore throat (n=93/9)	41 (44.1)	3 (33.3)	0.728				
Anosmia (n=90/10)	39 (43.3)	3 (30.0)	0.513				
Agueusia (n=86/8)	39 (45.4)	3 (37.5)	0.728				
Nausea and/or vomiting (n=90/9)	13 (14.4)	1 (11.1)	1				
Diarrhoea (n=100/9)	28 (28.0)	3 (33.3)	0.712				
Abdominal pain (n=39/5)	6 (15.4)	1 (20.0)	1				
Number of symptoms (tertile; n=145/17)			0.379				
≤4	76 (52.4)	7 (41.2)					
5	26 (17.9)	2 (11.8)					
>5	43 (26.7)	8 (47.0)					
Number of systemic symptoms (median; n=145/17)			0.009		0.022		0.011
≤1	55 (37.9)	1 (5.9)		1 (ref)		1 (ref)	
≥2	90 (62.1)	16 (94.1)		13.82 [1.45-131.88]		38.61 [2.30-647.40]	

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Number of ENT symptoms (tertile; n=145/17)			0.378				
0	48 (33.1)	7 (41.2)					
1	47 (32.4)	7 (41.2)					
>1	50 (34.5)	3 (17.6)					
Clinical examination							
Temperature>38°C			0.051		0.082		
No	84 (57.2)	7 (38.9)		1 (ref)			
Yes	13 (8.8)	5 (27.8)		5.16 [1.20-22.30]			
Not reported or missing	50 (34.0)	6 (33.3)		1.27 [0.36-4.49]			
Respiratory rate (per minute) (n=32/5)	18.5 [16-20]	21 [20-24]	0.058	1.14 [0.97-1.34]	0.103		
SaO2 (%) (n=85/10)	98 [97-99]	94.5 [90-98]	0.002	0.28 [0.09-0.91]	0.034		
Abnormalities in a lung examination			0.126		0.179		0.057
No	82 (55.8)	7 (38.9)		1 (ref)		1 (ref)	
Yes	12 (8.2)	4 (22.2)		4.33 [0.92-20.37]		15.39 [1.61-146.77]	
Not reported or missing	53 (36.0)	7 (38.9)		1.55 [0.47-5.17]		2.63 [0.52-13.34]	

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

a The p-values were obtained from a chi-squared test or Fisher's exact test for qualitative variables, and from the Mann-Whitney test for quantitative variables

b Multilevel logistic regression; the multivariate model included the following variables: age > 70 and/or presence of at least one comorbidity. number of systemic symptoms and abnormalities in a lung examination

ENT: ear nose throat; SaO_2: arterial oxygen saturation; OR: odds ratio; CI: confidence interval

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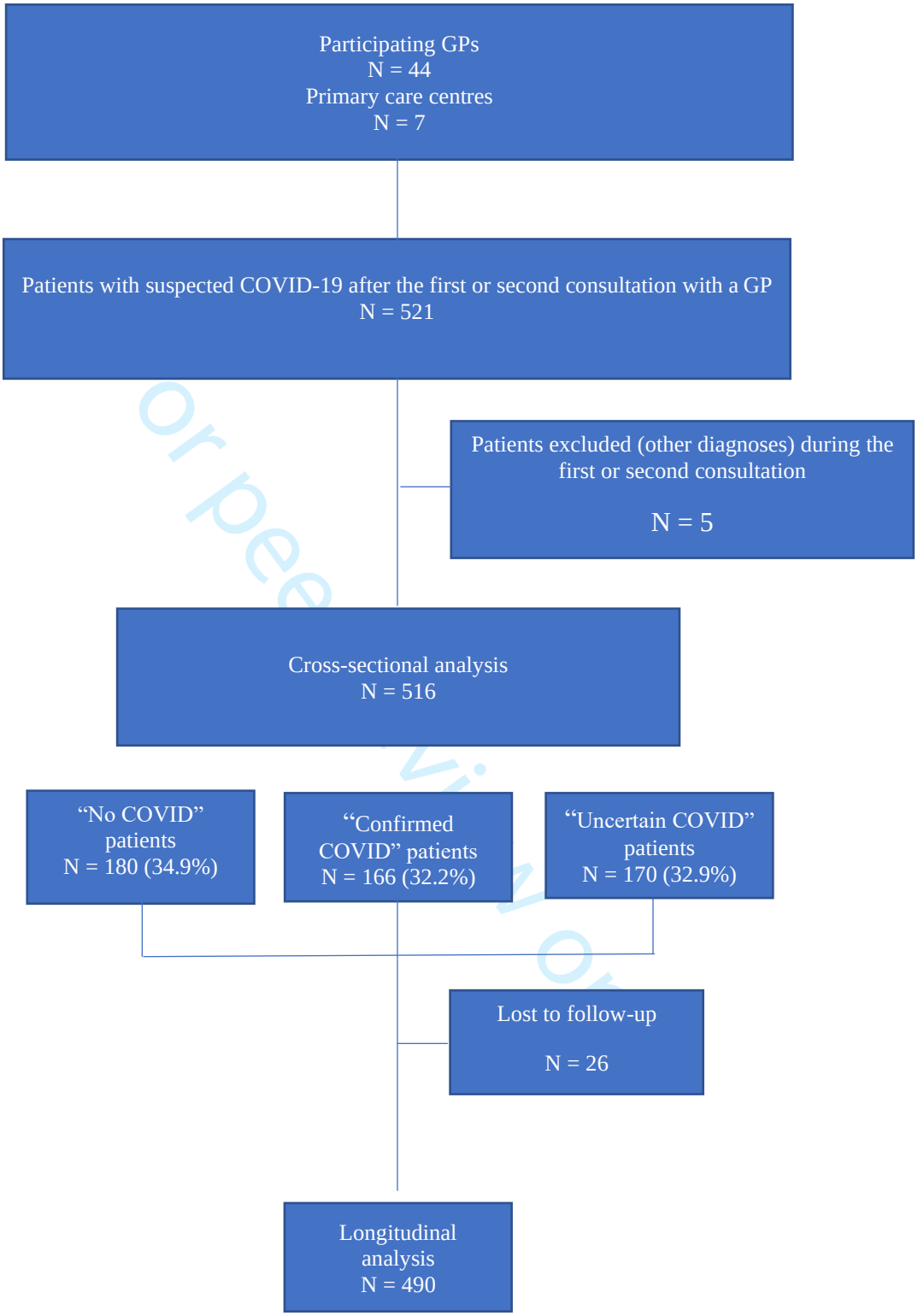
Figure 1. Study flow diagram



Online supplement 1. Table S1. Characteristics of the participating GPs and their practices

	Total n=44
Number of patients included per GP (median [IQR])	10.5 [3-24.5]
Number of participating GPs per centre	
MPCC Fontainebleau	6 (13.6)
CHC La Courneuve	6 (13.6)
MPCC Coulommiers	9 (20.5)
MPCC Epinay-sous-Sénart	5 (11.4)
MPCC Saint-Maur-des-Faussées	4 (9.1)
MPCC Torcy	10 (22.7)
MPCC Nemours	4 (9.1)
Age of GP (y) (median [IQR]) (n=42)	34 [32-42]
Sex	
Female	29 (65.9)
Male	15 (34.1)
Type of area in which the practice is located	
Rural	0 (0)
Semirural	9 (20.5)
Urban	35 (79.5)
State regulation of the GP's fees	
Yes	44 (100)
No	0 (0)
Secretarial support	38 (86.4)
Secretary at the practice	38 (86.4)
Phone line only	17 (38.6)
Appointments made online	21 (47.7)
Changes in consultation procedures since the COVID-19 epidemic	
Changes	38 (86.4)
No changes	6 (13.6)
Dedicated COVID-19 centre	10 (22.7)
Creation of specific COVID-19 consultations	38 (86.4)
Cancellation of non-COVID-19 consultations	13 (29.6)
Creation of separate COVID-19/non-COVID-19 areas	29 (65.9)
Changes to secretarial support since the COVID-19 epidemic	15 (34.1)
Closure of the secretary's office	6 (13.6)
Phone line only	18 (40.9)
Appointments made online	20 (45.5)
Changes to the waiting room since the COVID-19 epidemic	
No changes	0 (0)
Dedicated areas or arrangements in the waiting room	44 (100)
Closure of the waiting room	0 (0)
Hygiene measures introduced since the COVID-19 epidemic	
More frequent disinfection of reception areas	44 (100)
Alcohol-based hand sanitizer available for patients	44 (100)
Patients provided with face masks if required	39 (88.6)
Protective measures for caregivers since the COVID-19 epidemic	
Gowns	26 (59.1)
Masks	44 (100)
Overshoes	22 (50.0)
Gloves	31 (70.5)
Glasses	31 (70.5)
Hair nets	26 (59.1)

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

GP, general practitioner; MPCC : multiprofessional primary care centre; CHS : community health centre

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Online supplement 2. Table S2. Characteristics of the test results for the three groups of patients

	Total n=516	No COVID-19 n=180	Confirmed COVID-19 n=166	Uncertain COVID-19 n=170	p*
PCR test					<0.001
Not performed or missing result	386 (74.8)	116 (64.4)	100 (60.2)	170 (100)	
Negative	77 (14.9)	64 (35.6)	13 (7.8)	0 (0)	
Positive	53 (10.3)	0 (0)	53 (31.9)	0 (0)	
Serology test					<0.001
Not performed or missing result	232 (45.0)	27 (15.0)	35 (21.1)	170 (100)	
Negative	155 (30.0)	153 (85.0)	2 (1.2)	0 (0)	
Positive	129 (25.0)	0 (0)	129 (77.7)	0 (0)	
Chest CT scan					<0.001
Not performed or missing result	474 (91.9)	169 (93.9)	135 (81.3)	170 (100)	
Negative	13 (2.5)	11 (6.1)	2 (1.2)	0 (0)	
Suggestive	29 (5.6)	0 (0)	29 (17.5)	0 (0)	
Patient classification					
Positive PCR and serology tests	20 (3.9)	0 (0)	20 (12.0)	0 (0)	
Positive PCR test	33 (6.4)	0 (0)	33 (19.9)	0 (0)	
Positive serology test	109 (21.1)	0 (0)	109 (65.7)	0 (0)	
Suggestive chest CT	4 (0.8)	0 (0)	4 (2.4)	0 (0)	
Negative PCR and/or serology test	180 (34.9)	180 (100)	0 (0)	0 (0)	
No results	170 (32.9)	0 (0)	0 (0)	170 (100)	

Data are quoted as the n (%).

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Appendix 1. Characteristics of the study population and univariate comparison of the three patient groups (N=516)

	Total n=516	No COVID n=180 (34.9%)	Confirmed COVID n=166 (32.2%)	Uncertain COVID n=170 (32.9%)	p[a]	Confirmed COVID vs no-COVID OR [95% CI]	p[b]	Confirmed COVID vs uncertain COVID OR [95% CI]	p[b]
Age (years) (median, IQR)	43 [33-56]	45 [35-56.5]	49 [39-59]	36 [29-49]	<0.001	1.02 [1.01-1.03]	0.027	1.04 [1.03-1.06]	<0.001
Male sex	195 (37.8)	61 (33.9)	58 (34.9)	76 (44.7)	0.074	0.99 [0.63-1.56]	0.957	0.58 [0.36-0.93]	0.046
Caregivers (n=463/165/149/149)	58 (12.5)	17 (10.3)	31 (20.8)	10 (6.7)	0,001	2.70 [1.39-5.24]	0.003	5.58 [2.50-12.46]	<0.001
Contact with confirmed positive case (n=290/96/98/96)					<0.001		0.006		<0.001
No	130 (44.8)	48 (50.0)	30 (30.6)	52 (54.2)		1 (ref)		1 (ref)	
Yes	67 (23.1)	19 (19.8)	36 (36.7)	12 (12.5)		3.48 [1.62-7.51]		8.77 [3.59-21.46]	
Uncertain	93 (32.1)	29 (30.2)	32 (32.7)	32 (33.3)		1.95 [0.95-4.01]		2.59 [1.22-5.51]	
Smoking (n=159/62/52/45)	64 (40.3)	28 (45.2)	16 (30.8)	20 (44.4)	0.235				
At least one comorbidity (n=509/178/164/167)	207 (40.7)	85 (47.8)	77 (47.0)	45 (27.0)	<0.001	0.84 [0.52-1.31]	0.416	1.67 [1.01-2.79]	0.092
Dyslipidaemia (n=509/178/164/167)	16 (3.1)	8 (4.5)	7 (4.3)	1 (0.6)	0.071	0.73 [0.24-2.18]	0.570	3.11 [0.36-27.18]	0.57
Obesity (n=173/59/59/55)	67 (38.7)	25 (42.4)	23 (39.0)	19 (34.6)	0.692				
Hypertension (n=509/178/164/167)	70 (13.8)	25 (14.0)	29 (17.7)	16 (9.6.)	0.100	1.05 [0.54-2.03]	0.882	0.88 [0.42-1.88]	0.882
Diabetes (n=509/178/164/167)	31 (6.1)	18 (10.1)	7 (4.3)	6 (3.6)	0.020	0.28 [0.11-0.73]	0.018	0.62 [0.19-2.00]	0.423
Cardiovascular disease (n=509/178/164/167)	33 (6.5)	9 (5.1)	16 (9.8)	8 (4.8)	0.117	1.81 [0.73-4.45]	0.398	0.94 [0.36-2.48]	0.903
Asthma (n=509/178/164/167)	52 (10.2)	19 (10.7)	15 (9.2)	18 (10.8)	0.859				
COPD (n=509/178/164/167)	9 (1.8)	6 (3.4)	0 (0)	3 (1.8)					
Venous thromboembolism (n=509/178/164/167)	7 (1.4)	4 (2.3)	1 (0.6)	2 (1.2)					
Inflammatory rheumatic disease (n=509/178/164/167)	9 (1.8)	4 (2.3)	2 (1.2)	3 (1.8)					
Cancers (n=509/178/164/167)	13 (2.6)	8 (4.5)	4 (2.4)	1 (0.6)	0.059	0.48 [0.14-1.69]	0.407	2.61 [0.27-25.37]	0.407
Autoimmune diseases (MS, UC, Crohn's, SLE, sarcoidosis, Basedow etc.) (n=509/178/164/167)	15 (3.0)	10 (5.6)	4 (2.4)	1 (0.6)	0.015	0.33 [0.10-1.13]	0.154	3.03 [0.32-28.38]	0.332
Age > 70 and/or presence of at least one comorbidity (n=509/178/164/167)	210 (41.2)	85 (47.8)	78 (47.6)	47 (28.1)	<0.001	1.03 [0.67-1.59]	0.899	2.33 [1.45-3.74]	<0.001
Mode of consultation (n=515/179/166/170)					0.526				
Face-to-face	345 (67.0)	125 (69.8)	114 (68.7)	106 (62.4)					
Teleconsultation	157 (30.5)	50 (27.9)	48 (28.9)	59 (34.7)					
Phone	10 (1.9)	4 (2.3)	2 (1.2)	4 (2.3)					
Home visit	3 (0.6)	0 (0)	2 (1.2)	1 (0.6)					
Symptoms at the initial consultation									
Fever or feeling feverish (n=469/158/151/160)	200 (42.6)	68 (43.0)	81 (53.6)	51 (31.9)	0.001	1.58 [0.99-2.53]	0.058	2.15 [1.31-3.52]	0.004
Asthenia (n=184/74/61/49)	145 (78.8)	56 (75.7)	50 (82.0)	39 (79.6)	0.665				
Muscle ache (n=370/117/123/130)	219 (59.2)	67 (57.3)	85 (69.1)	67 (51.5)	0.015	1.63 [0.95-2.80]	0.074	1.91 [1.11-3.29]	0.04
Headache (n=358/121/108/129)	216 (60.3)	76 (62.8)	59 (54.6)	81 (62.8)	0.349				

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Rhinorrhoea (n=366/126/109/131)	194 (53.0)	75 (59.5)	56 (51.4)	63 (48.1)	0.171				
Cough (n=471/163/149/159)	366 (77.7)	127 (77.9)	119 (79.9)	120 (75.5)	0.649				
Expectorations (n=265/80/80/105)	61 (23.0)	17 (21.3)	18 (22.5)	26 (24.8)	0.846				
Chest pain (n=325/107/103/115)	80 (24.6)	39 (36.5)	19 (18.5)	22 (19.1)	0.002	0.40 [0.21-0.77]	0.012	0.97 [0.48-1.98]	0.94
Dyspnoea at rest and/or on exertion (n=370/131/116/123)	128 (34.6)	56 (42.8)	35 (30.2)	37 (30.1)	0.051	0.56 [0.32-0.96]	0.07	1.09 [0.61-1.96]	0.77
Sore throat (n=351/122/102/127)	177 (50.4)	73 (59.8)	44 (43.1)	60 (47.2)	0.030	0.50 [0.29-0.88]	0.032	0.91 [0.53-1.58]	0.746
Anosmia (n=317/109/100/108)	74 (23.3)	11 (10.1)	42 (42.0)	21 (19.4)	<0.001	7.11 [3.30-15.29]	<0.001	3.74 [1.91-7.31]	<0.001
Agueusia (n=282/89/94/99)	75 (26.6)	13 (14.6)	42 (44.7)	20 (20.2)	<0.001	4.79 [2.31-9.93]	<0.001	3.38 [1.73-6.59]	<0.001
Nausea and/or vomiting (n=343/120/100/123)	50 (14.6)	19 (15.8)	15 (15.0)	16 (13.0)	0.815				
Diarrhoea (n=360/127/110/123)	84 (23.3)	33 (26.0)	32 (29.1)	19 (15.5)	0.033	1.21 [0.68-2.17]	0.513	2.58 [1.31-5.07]	0.012
Abdominal pain (n=143/57/44/42)	19 (13.3)	7 (12.3)	7 (15.9)	5 (11.9)	0.826				
Number of symptoms (tertile; n=511/179/163/169)					0.528				
≤3	181 (35.4)	68 (38.0)	49 (30.1)	64 (37.9)					
4-5	184 (36.0)	62 (34.6)	62 (38.0)	60 (35.5)					
>5	146 (28.6)	49 (27.4)	52 (31.9)	45 (26.6)					
Number of systemic symptoms (tertile; n=511/179/163/169)					0.020				
≤1	216 (42.3)	82 (45.8)	56 (34.3)	78 (46.2)		1 (ref)	0.100	1 (ref)	0.072
2	142 (27.8)	40 (22.4)	49 (30.1)	53 (31.4)		1.80 [1.04-3.11]		1.19 [0.69-2.05]	
>2	153 (29.9)	57 (31.8)	58 (35.6)	38 (22.5)		1.42 [0.85-2.37]		1.83 [1.04-3.22]	
Number of ENT symptoms (tertile; n=511/179/163/169)					0.277				
0	182 (35.6)	62 (34.6)	55 (33.7)	65 (38.5)					
1	188 (36.8)	75 (41.9)	55 (33.7)	58 (34.3)					
>1	141 (27.6)	42 (23.5)	53 (32.6)	46 (27.2)					
Clinical examination									
Temperature>38°C					0.012		0.343		<0.001
No	325 (63.0)	110 (61.1)	92 (55.4)	123 (72.4)		1 (ref)		1 (ref)	
Yes	39 (7.6)	15 (8.3)	18 (10.8)	6 (3.5)		1.52 [0.71-3.24]		4.09 [1.48-11.30]	
Not reported or missing	152 (29.4)	55 (30.6)	56 (33.7)	41 (24.1)		1.35 [0.83-2.20]		2.30 [1.35-3.91]	
Respiratory rate (per minute) (n=101/41/38/22)	18 [16-20]	18 [16-20]	20 [17-20]	18 [16-20]	0.387				
SaO2 (%) (n=272/91/96/85)	98 [97-99]	98 [97-99]	98 [97-99]	98 [97-99]	0.153				
Abnormalities in a lung examination					0.585				
No	270 (52.3)	94 (52.2)	90 (54.2)	86 (50.6)					
Yes	48 (9.3)	20 (11.1)	16 (9.7)	12 (7.1)					
Not reported or missing	198 (38.4)	66 (36.7)	60 (36.1)	72 (42.3)					

Data are quoted as the n (%) for qualitative variables and the median [IQR] for quantitative variables

a The p-values were obtained from a chi-squared test or Fisher's exact test for qualitative variables and from the Kruskal Wallis test for quantitative variables

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b Age-adjusted multilevel multinomial logistic regression; p-values of paire-wise comparisons were corrected by the False discovery rate method

COPD: chronic obstructive pulmonary disease; MS: multiple sclerosis; UC:. ulcerative colitis; SLE: systemic lupus erythematosus; ENT: ear nose throat; SaO_2: arterial oxygen saturation; OR: odds ratio; CI: confidence interval

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	Tables
		(*d*) If applicable, explain how loss to follow-up was addressed	Figure 1
		(*e*) Describe any sensitivity analyses	8
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	25
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Tables
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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